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The Bedside Diagnosis of Pericardial Effusion

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Physical diagnosis has long since degenerated into a largely meaningless ritual to which some present-day clinicians render only reluctant and impatient lip service. As Garrison pointed out nearly thirty years ago, "the time-honored Hippocratic reliance on the natural powers of the mind and the five senses in diagnosis (without which the physician is nothing)" has been replaced to a disquieting extent by "an almost bewildering array of laboratory tests, instrumentation, specialism, and etiological theorizing . . . which tend to merge bedside medicine into the ancillary devices it utilizes, to enslave the mind of the physician by making him dependent upon artificial aids and, *in extremis*, to turn the patient himself into a laboratory animal. Between the two lies the Golden Mean, the *via media* followed by all practitioners of sound sense, ripe judgment, and varied experience."

This report indicates how, by utilizing simple clinical observations, one of which was made two hundred years ago, and sound physiologic and physical principles, pericardial effusion may be readily diagnosed at the bedside.

ANATOMY

A few facts concerning the anatomy of the pericardium are pertinent to a discussion of the physical signs of pericardial effusion.

The fibrous parietal layer becomes continuous with the adventitia of the great vessels. The serous visceral layer is invaginated by the heart, and sinuses are formed at the roots of the great vessels. The anterior aspect of the pericardium is attached by loose connective tissue to the left half of the lower part of the sternum and to the fourth, fifth, and sixth left costal cartilages. Inferiorly it attaches to the central tendon of the diaphragm and to the muscle on both sides of the central tendon.

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PHYSICAL SIGNS OF PERICARDIAL EFFUSION

Transverse Diameter.—The extent of the transverse diameter is ascertained by immediate percussion with the patient in the sitting position. The patient must be sitting because the supine position causes accumulation of the fluid posteriorly. Immediate, or definitive, percussion must be employed because it provides the smallest possible pleximeter area. The method requires a penetrating, damping blow with the distal third of the volar surface of the middle finger. Mediate, or sonorous, percussion, because of the necessarily firm application of the pleximeter finger, inevitably and invariably includes so large an area of the chest wall in the pleximeter, regardless of how light the blow struck by the plexor, that it is useless for defining the borders of dense bodies within the thorax. The right border is sought by percussing toward the precordia in the second, third, fourth, and fifth intercostal spaces, beginning at the anterior axillary line. Rotch's sign of pericardial effusion, namely, conversion of the normally acute cardiohepatic angle of dullness to an obtuse angle, is unreliable. The examiner seeks the location of the left border by definitive percussion, beginning at the midscapular line. If the effusion is large, the lower lobe of the left lung may be displaced and compressed posteriorly, with the result that percussion cannot distinguish between the dullness of the compressed lung and that of the effusion.

Anteroposterior Diameter.—The outstanding feature of the anterior aspect, i.e., the precordia, is the conspicuous absence of visible and palpable activity in spite of the unusually extensive transverse diameter. The posterior aspect of the swollen pericardial sac itself is not directly accessible to palpation or percussion, but there may be signs in the infrascapular region of encroachment on the lower lobe of the left lung. If the encroachment is slight, relaxation of the remainder of the lobe takes place, producing Skodaic tympany, but, if the encroachment is extensive, Ewart's sign appears, namely, dullness and loud, high-pitched bronchial breathing, and *tactile fremitus becomes diminished or absent.* Diminution of the fremitus is brought about by partial or complete occlusion of the bronchi; aside from this, the signs are those of increased density of the lung, as would be expected. The examiner must beware of mistaking this condition for pneumonia.

Vertical Diameter.—At the superior aspect, dullness may extend to the second intercostal space in the parasternal lines, and, if the pericardial sinuses about the roots of the great vessels become filled with fluid, a dense, homogeneous medium is interposed between the chest wall and the tracheal air column. Thus, a tracheal tone, tracheal-tone change, and cracked-pot percussion note may be elicited. If the swollen pericardial sac encroaches upon the upper lobe of the left lung, there may be impairment of the normal undulatory movement of the second, third, fourth, and fifth ribs. Several physical signs indicate the location of the inferior aspect of the pericardial sac. Downward displacement of the central tendon and subcardial portion of the diaphragm both to the right and left of the midline is betrayed by vertebrad movement of the lower end of the sternum and symmetrical modification of the movement of the medial halves

of both costal margins. The latter may remain stationary or may be drawn toward the median line. In order to understand the significance of these phenomena, it is necessary to review the mechanics of breathing. The function of the diaphragm is to maintain by isometric contraction, or to enlarge by isotonic contraction and excursion, the vertical diameter of the thorax. In performing its function, the diaphragm exerts traction on the costal margins into which it is inserted, and, if this action were unopposed, the costal margins would be approximated with every inspiration (and this, incidentally, would be contrabiological). But the action of the scalenal-intercostal group of muscles with respect to the movement of the costal margins is diametrically opposed to that of the diaphragm, and the mechanical disadvantage under which the diaphragm labors is sufficient to enable the scalenal-intercostal muscles to overcome the action of the diaphragm and bring about inspiratory divergence of the costal margins. For the same reason, during inspiration the lower end of the sternum normally rotates cephalad around a transverse axis through the manubriosternal junction, but flattening of the anteromedian portion of the diaphragm modifies this normal cephalad movement, so that the xiphoid remains stationary or is drawn toward the vertebral column. These changes in direction of movement may be apparent to the eye, but they are better appreciated by palpation. Furthermore, changes in *vigor* of movement, which is equally as important as direction of movement, cannot be ascertained except by palpation. The diaphragm's mechanical disadvantage comes about as a result of the disparity between its actual anatomic line of traction and its theoretically ideal, or resultant, line of traction. The latter is a straight line drawn from the central tendon to the point of insertion in the costal margin. The greater the disparity, i.e., the longer the perpendicular dropped from the ideal line of traction to the most distant point of the anatomic curve, the greater the mechanical disadvantage of the diaphragm in its contest with the scalenal-intercostal muscles for control of the movement of the costal margins. As long as the innervation of the diaphragm remains intact, these signs of flattening of the subcardial diaphragm cannot fail.

The outstanding physical sign of pericardial effusion is downward rotation of the liver, which behaves as a lever of the third class. The displacement produced by pericardial effusion exceeds all others; seven hundred cubic centimeters may push the edge of the liver into the pelvis. Hepatic enlargement may also occur, either as one of the manifestations of venous stasis, or as a result of obstruction of the inferior vena cava where it passes through the diaphragm and pericardium. Enlargement of the liver leaves the organ in situ, with its edge and relatively flat anterior surface in immediate contact with the anterior abdominal wall, whereas downward rotation of the liver buries the edge deeply within the abdomen and brings forward the rounded dome in such a manner that it presents a swelling which is like a segment of a cylinder lying transversely across the epigastrium. This important sign was described in 1761, by Josef Leopold Auenbrugger,[1] the father of percussion. It is as nearly pathognomonic as any physical sign can be, but its significance—indeed, its very existence—has long been forgotten.

ADDITIONAL SIGNS OF PERICARDIAL EFFUSION

A pericardial friction may persist in the presence of a large effusion, and may be heard with the patient in one position and not heard with the patient in another.

The areas of phrenic referred tenderness, with or without pain, described by Noël François Odon Gueneau de Mussy,[2] in 1865, lie between the heads of the sternocleidomastoid muscles, near the umbilicus, and just lateral to the spine of the eleventh thoracic vertebra.

Pulsus paradoxus, which was first described by C. J. B. Williams,[3] in 1850, and which was elucidated definitively by Gauchat and Katz,[4] in 1924, may be defined as a periodic respiratory waxing and waning of the volume of the arterial pulse. During inspiration the pulse diminishes or disappears entirely, and returns again to normal during expiration. True pulsus paradoxus (1) is independent of any irregularity of the heartbeat, (2) is present in all accessible arteries, and (3) occurs without conscious effort on the part of the patient to modify his breathing. In pericardial effusion the mechanism of pulsus paradoxus is as follows: Normally, variations in intrapleural pressure during inspiration and expiration are transmitted without loss through the pericardium to the cardiac chambers. Consequently, the fall of intrathoracic pressure during inspiration affects intra-atrial and intraventricular pressure to the same degree as it does the pressure within the afferent extrapericardial pulmonary veins. Hence, the effective difference in pressure between veins and heart is not greatly altered by inspiration, the systolic discharge of the ventricles is practically unaffected, and no variation in pulse volume occurs; but when the sac is distended with fluid, respiratory variations of intrathoracic pressure cannot affect intracardiac pressure as much as the pressure in the pulmonary veins, and the greater the intrapericardial pressure, the greater the disparity. It is as though the pericardial contents become extrathoracic. During inspiration the normal pressure gradient from pulmonary veins to left atrium is upset, filling and discharge of the left ventricle are diminished, and pulsus paradoxus results. The amount of respiratory variation in pulse volume may be so slight that it cannot be detected without the use of the sphygmomanometer.

Inasmuch as pulsus paradoxus may be brought about by conditions other than pericardial effusion, such as pulmonary emphysema, bronchial asthma, massive pleural effusion, pneumothorax, and mediastinopericardial adhesions, it is significant only when it occurs in conjunction with other reliable signs of pericardial effusion.

Cardiac tamponade is arbitrarily excluded from this discussion.

The following report illustrates the typical physical signs in a case of pericardial effusion.

CASE REPORT*

J. R. C. (VAH 3420), a 46-year-old man, was admitted to the Medical Service on Nov. 14, 1952, with a history of recurrent migratory polyarthritis. Physical examination was negative,

*Permission to use this case report was kindly granted by the Chief of the Medical Service, Veterans Administration Hospital, Iowa City, Iowa.

with the exception of evidence of rheumatoid arthritis, pansinusitis, and varicose veins. A teleoroentgenogram showed a well-circumscribed hilar mass on the left side. Bronchoscopic and direct laryngoscopic examination revealed no abnormality. The bronchogram on the left side was normal. Acid-fast bacilli were found in smears of bronchial and gastric washings, but cultures were negative. Cells which were thought to be malignant were found in the bronchial washings. Biopsy of a right axillary lymph node suggested the possibility of giant follicular lymphoma, but this was by no means certain. The patient refused to undergo exploratory thoracotomy, and was discharged on Jan. 15, 1953.

He was readmitted on April 15, 1953. The physical signs were essentially the same, except that early elevation of the roots of the fingernails and toenails was noted. Radiologic examination showed a minimal degree of hypertrophic pulmonary osteoarthropathy. There was roentgenographic evidence of an increase in the size of the hilar mass. Thoracotomy was performed on the left side on May 28, 1953, and the hilar mass was biopsied. The pathologist reported "undifferentiated malignant tumor." The left hilar area was subjected to moderate doses of irradiation, and the patient was discharged on June 15, 1953.

The patient was admitted for the last time on Oct. 14, 1953, with complaints of chills, fever, cough, slight hoarseness, and a forty-pound loss of weight. A minimal degree of cyanosis was present. The pertinent physical signs were confined to the chest. The right side of the thorax was larger than the left. The trachea was in the midline, and no abnormal physical signs were present over the right lung. There was abnormal dullness in the cardiohepatic angle; it began 2 cm. from the right border of the sternum. Dullness was present along the thoracotomy scar and at the inferior tip of the left scapula. The medial halves of the costal margins and the lower end of the sternum remained stationary during inspiration. Auscultation revealed fine, scattered râles and whispered pectoriloquy throughout the left lung. Bronchial breathing was heard at the inferior edge of the left scapula, but there was no accompanying increase in tactile fremitus. The heart sounds were decreased in intensity, and there was no accentuation of the second heart sound in the pulmonic area. Loud systolic and diastolic scratching noises were heard over the heart, but there were no murmurs. Pulsus paradoxus was present, with a spread of 15 mm. Hg between the appearance of the first Korotkov sound and the level of equal intensity of all the Korotkov sounds. Inspection of the abdomen showed a swelling which resembled a segment of a cylinder lying transversely across the epigastrium. The liver moved with respiration; it was neither tender nor nodular. The edge could not be palpated because of the rotation of the liver. There was no change in any of the physical signs when the patient changed his position. A diagnosis of pericarditis and pericardial effusion was made. Repeated pericardiocenteses produced 150 c.c. of serosanguinous fluid. The patient's condition grew steadily worse, and he died on Nov. 22, 1953.

Autopsy.—The left lung weighed 1,300 grams. The tumor involved the left lung extensively, with minimal metastases to the lateral portion of the left half of the diaphragm. A small abscess in the left upper lobe extended into the left pleural cavity. It was well localized. The visceral pericardium was the seat of fibrinous inflammation, and the pericardial cavity contained 200 c.c. of bloody fluid. Metastases were found in the subepicardial adipose tissue. The phrenic nerves were not involved, and there were no metastases in the liver.

COMMENT

This report is made specifically to analyze and re-emphasize the basic principles in the bedside diagnosis of pericardial effusion.

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Clinical Pharmacology of Flumethiazide, A Diuretic Agent

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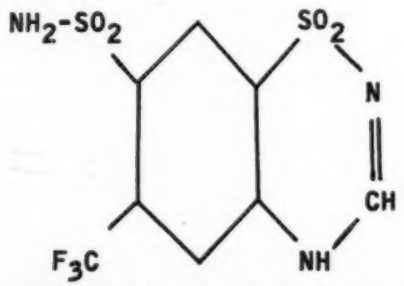
INTRODUCTION

The list of diuretic agents grows longer. It is of some interest to correlate chemical structure with pharmacodynamic action. It is of even greater interest to find practically identical pharmacologic effects in a compound which has been modified by shifting one of its halogen radicals. The latter is the case with the compound under consideration, flumethiazide.* This compound differs from chlorothiazide only in the presence of a trifluoromethyl group instead of a chloride group (Fig. 1). This suggests that its diuretic capabilities reside in the basic heterocyclic ring rather than in the halogen radical. Investigation of this drug in the laboratory animal revealed it to have certain natriuretic and diuretic properties.[1]

FLUMETHAZIDE



6-(trifluoromethyl)-1,4,2-benzothiadiazine-7-sulfonamide, 1,1-dioxide

Fig. 1.—The structural formula for flumethiazide is the same as that for chlorothiazide, except that the chloride is replaced by a trifluoromethyl group.

The purpose of the present communication is to report the clinical pharmacology of flumethiazide as a diuretic agent. Subsequent communications will show its clinical utility in various types of edema,[2] and its use as an adjunct in the therapy of hypertension.[3]

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*Flumethiazide is 6-(trifluoromethyl)-1, 4, 2-benzothiadiazine-7-sulfonamide, 1, 1-dioxide. Available as Ademol from E. R. Squibb & Sons.

MATERIALS AND METHODS

A pilot study of flumethiazide was undertaken to determine the dose response curve, using previously described techniques for the bioassay of diuretics.[4] Briefly described, the subjects of this study were 10 men with hypertensive cardiovascular disease who were maintained on an air-conditioned metabolic ward. They ate a diet which contained 50 mEq. of sodium, and drank 3,000 ml. of distilled water per day. All medications other than diuretics necessary for the control of their congestive heart failure were maintained. At the time of the study they were free of detectable edema. Twenty-four-hour urines were collected and analyzed for sodium and volume. The subjects' weights were obtained prior to breakfast and after voiding. The particular dose of the drug was given at 6 A.M. each morning. The dose of flumethiazide was given in progressively incremental amounts, beginning with 0.25 Gm. and extending to 0.5, 1.0, 2.0, and 4.0 Gm. as a single dose. Each dose was given five times.

After the significant points of the dose response curve were established by pilot study, namely, between 1.0 and 2.0 Gm., the drug was administered at both of these doses to each subject of the study, and the previously described observations were made.

These data were then subjected to the statistical analysis of variance for determination of significance, and a computation of the "potency estimation" was made. Next, these data were compared to the standard diuretic meralluride (Mercuhydrin), which has a potency estimation of "one."

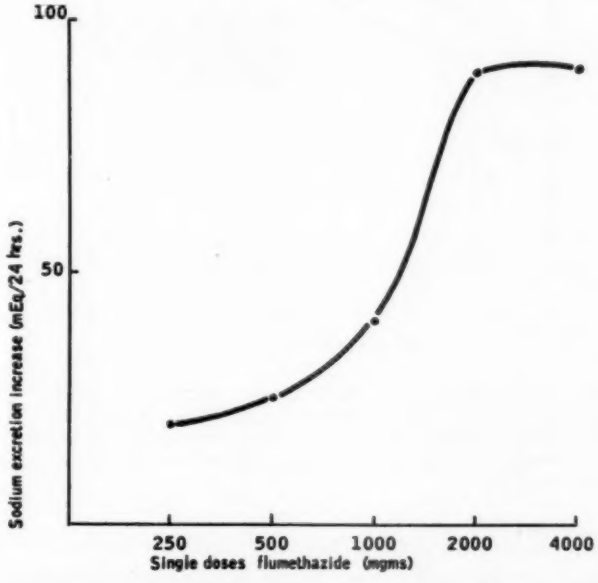

Fig. 2.—Dose response curve of flumethiazide. Observations on 5 patients at each dose indicates that the effective range of the sodium response dose is between 0.25 and 2.0 Gm. (as a single dose). The difference in the excretion of sodium between the doses of 1.0 and 2.0 Gm. is statistically significant.

The effects of the excretion of electrolytes were then studied following the administration of flumethiazide in 5 different patients. These studies consisted of the analysis of the urine for volume, sodium, potassium, ammonia, pH, chloride, bicarbonate, tritratable acidity, and total solute in six fractional periods during the 24 hours following the administration of 1.0 Gm. of flumethiazide (three consecutive 2-hour periods followed by three consecutive 6-hour periods).

The drug was then administered at a dose of 1.0 Gm. daily to 5 patients for five consecutive days. The urine was analyzed for sodium and volume, and the blood was analyzed for significant changes in electrolytes (sodium, potassium, chloride, bicarbonate, urea nitrogen, and hematocrit). The purpose of this study was to determine whether the drug is repetitively effective and whether tolerance to the drug develops, as well as to evaluate the drug's effects on the biochemical architecture.

RESULTS

1. *Dose Response Curve.*—The pilot study revealed that there was a slight increase in the excretion of sodium beginning with even the smallest dose (0.25 Gm.), but that the significant part of the response curve was between a dose of 1.0 and 2.0 Gm. Although the dose of 4.0 Gm. was not associated with any evidence of clinical toxicity, the excretion of sodium did not increase significantly beyond that observed with a dose of 2.0 Gm. (Fig. 2).

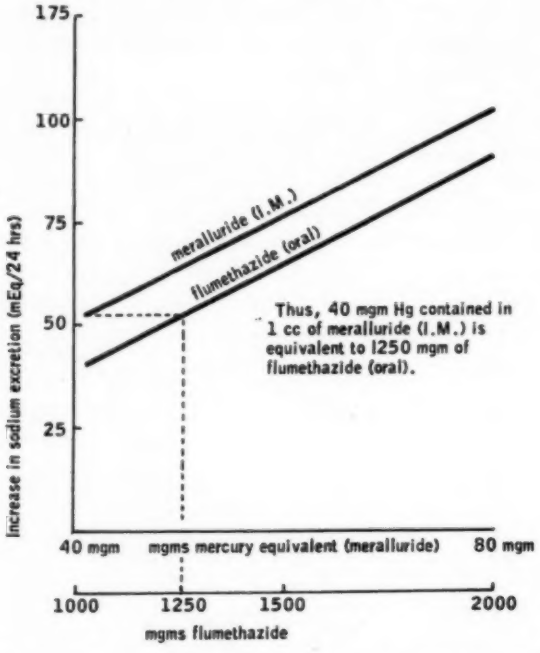

Fig. 3.—Comparison of the dose response curve for meralluride (Mercuhydrin), the "standard" with a potency estimation of "one" (after parenteral administration), with that for flumethiazide indicates that the potency of flumethiazide is "0.7." Direct reading of the graph indicates that 1 c.c. of meralluride (I.M.) is equivalent to 1.25 Gm. of flumethiazide (orally) in the ability to produce an increase in the excretion of sodium.

Ten observations at two doses (1.0 and 2.0 Gm.) revealed that there was a significant increase in the volume of urine and urinary sodium, and a decrease in weight (Table I). The average increase in urinary sodium was 40 mEq. per 24 hours over control at a dose of 1.0 Gm. At a dose of 2.0 Gm. the average increase was 90 mEq. per 24 hours over control. These data, of course, are paralleled by changes in volume of urine and loss of weight.

After the data had been subjected to an analysis of variance, it was found that the dose response curves for flumethiazide and meralluride are parallel and linear, and that the error is not significant (Fig. 3). By direct reading of the curve it is seen that a dose of 1.0 c.c. of Mercuhydrin administered parenterally (containing 40 mg. of mercury) is equivalent in natriuretic potency to 1.25 Gm. of flumethiazide administered orally. The data reveal that the potency estimation of flumethiazide is 0.7 when meralluride is 1.0. In other words, flumethiazide is 70 per cent as potent as meralluride at the two doses under observation.

2. *Pattern of Excretion of Electrolytes.*—The composite pattern of excretion of electrolytes (Fig. 4) demonstrates that there is an increase in the excretion of all moieties except ammonia during the second 2-hour period following the administration of the drug. These changes persisted at a lower level for at least 12 hours, returning to control levels 18 hours after the drug was given. Excretion of ammonia was characterized by a compensatory decrease during the period of drug response and a slight increase at the end of the 24-hour period. The most significant increases in the rates of excretion were observed for sodium and chloride, which showed a threefold to fivefold change, while the increase in the excretion of potassium was about one-half or less that of sodium and chloride. The rate of excretion of bicarbonate increased to a maximum at the end of 6 hours, but the average total excretion over the 24-hour period was small. No significant alteration in the excretion of phosphate or titratable acidity was observed. The pH of the urine increased slightly during the first 12 hours.

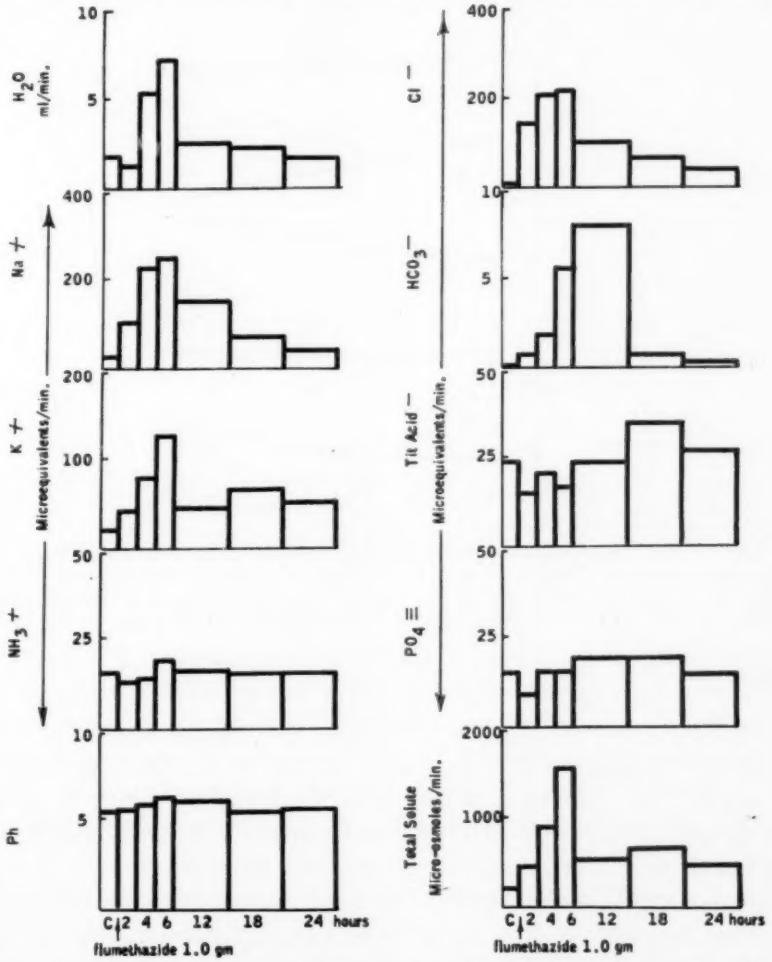

Fig. 4.—Composite patterns of excretion following the administration of 1.0 Gm. of flumethiazide, orally, at 6 A.M. The pattern of excretion of electrolytes (average of 5 patients given 1.0 Gm. of flumethiazide as a single dose) is practically identical to that observed following the administration of chlorothiazide. There is a prompt onset (2 hours) of diuresis, with the greatest changes observed in sodium and chloride. Excretion of potassium and bicarbonate is increased, but in fairly physiological proportions.

3. *Diuretic and Biochemical Effects Associated With Daily Administration of Flumethiazide.*—There was a continuing excretion of sodium following daily therapy with flumethiazide until the body stores were depleted. (These patients were eating a diet containing only 50 mEq. of sodium per day.) A very minimal rise in blood urea nitrogen was observed. There was a tendency to slight elevation of the carbon-dioxide combining power, but this was moderate and not clinically significant. Changes in sodium, potassium, and chloride were not significant (Fig. 5).

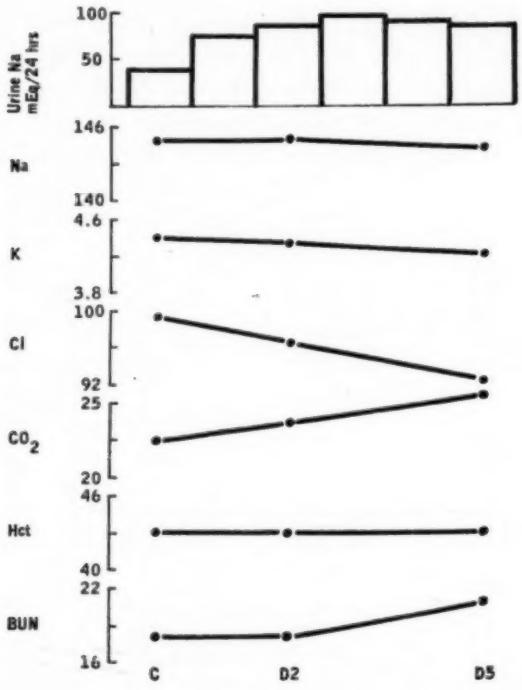

Fig. 5.—Diuretic and biochemical effects associated with the daily administration of flumethiazide (1.0 Gm. daily for 5 consecutive days). There is a continuing response in the excretion of sodium until the body stores are depleted. There is a tendency toward the development of hypochloremic alkalosis.

DISCUSSION

Flumethiazide (Ademol) is an interesting compound in that it differs structurally from chlorothiazide only by the presence of a trifluoromethyl group in the place of chloride. In spite of this shift in a radical there is no significant pharmacologic difference between the two compounds, based upon the results of the current study. Both drugs are of extreme value as diuretic agents because (1) they can be administered orally, (2) they are repetitively effective (that is, tolerance does not develop), and (3) they are virtually free of acute toxicity. The changes in biochemical architecture following the administration of this drug is similar to those following the administration of chlorothiazide; there is a tendency toward hypochloremic alkalosis. While the potency estimation of flumethiazide is 0.7, the potency estimation of chlorothiazide is 0.8. That is

they are 70 and 80 per cent, respectively, as potent as meralluride (Mercuhydrin) parenterally administered. Subjecting these data to a simple Student's "t" test revealed no significant difference between the natriuretic potency of the two orally effective compounds.

A more critical evaluation of the electrolyte and urinary volume relationships of these two compounds suggests that flumethiazide may have a greater effect on the excretion of water than does chlorothiazide. Expressed in another way, it is suggested that in doses producing equivalent diuresis (increase of water), the excretion of sodium is only 70 per cent as great.

Thus, the basic clinical pharmacologic studies of flumethiazide in human beings suggest that this drug may be of extreme value in the treatment of various states of edema,[2] and, perhaps, as an adjunct in antihypertensive therapy.[3]

TABLE I. DIURETIC RESPONSES TO SINGLE DOSES OF FLUMETHIAZIDE

	AVERAGES OF DETERMINATIONS ON 10 PATIENTS							
	1.0 GM. DOSE				2.0 GM. DOSE			
	C	D	I	P VALUE*	C	D	I	P VALUE
Urine Volume (L./24 hr.)	3.0	3.3	0.3	.01	3.0	3.5	0.5	.01
Urine Sodium (mEq./24 hr.)	45	85	40	.001	45	135	90	.001
Body Weight (Kg.)	65	64.6	−0.4	.01	65	64.2	−0.8	.01

*P value: Determined from Student's "t" test.
C: Control. D: Drug. I: Increase.

CONCLUSIONS

Flumethiazide has been subjected to study by clinical pharmacologic techniques, with attention to its action as a diuretic agent. The results revealed that it is not significantly different from chlorothiazide in its diuretic potency or in its ability to produce changes in biochemical architecture. Furthermore, the drug is repetitively effective on daily use. The initial data, therefore, suggest that flumethiazide is of potential value in the long-term management of various states of edema, and, perhaps, as an adjunct in the therapy of hypertension.

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The Effects of SU-5879 (Esidrix*) in Congestive Heart Failure and Hypertension: A Clinical Evaluation

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The most significant recent advance in the therapy of edema has been the introduction and use of the newly developed sulfonamide derivatives. The first of these was acetazoleamide,[1,2] which produces diuresis by the inhibition of carbonic anhydrase. More effective diuretic action results from chlorothiazide,[3,4] which also inhibits carbonic anhydrase, but augments urinary output in a manner similar to the mercurials. Furthermore, chlorothiazide has been shown to be of considerable value as an antihypertensive agent.[5]

Su-5879 (Ciba), or hydrochlorothiazide, was synthesized in the search for new and possibly more effective diuretic and antihypertensive drugs in the sulfonamide group. It is closely related to chlorothiazide, as shown in Fig. 1. Preliminary experiments[6] showed Su-5879 to be from 7 to 16 times as active as chlorothiazide in producing diuresis in the dog and rat, although only one ninth as potent in its capacity to inhibit carbonic anhydrase. It also appeared to have a longer duration of diuretic action in equipotent dosage, and less potassium dissipating effect.

METHOD OF STUDY

We have determined the effects of Su-5879 on the electrolyte patterns in the urine and plasma during clinical diuresis in 19 hospitalized and 20 outclinic patients with edema due to congestive heart failure. Each of our inpatients was begun with a control period of 3 to 4 days, during which the regimen of therapy for the congestive heart failure was kept constant, a low-sodium diet (500 mg.) was administered, and all other diuretic agents and potassium were withheld. During this period there was careful clinical evaluation, with complete blood count, urinalysis, and determination of daily body weight, venous pressure, blood urea nitrogen (BUN), and serum Na, K, Cl, and CO_2. Specimens of urine were collected and measured, and the content of Na, K, and Cl was determined for a 12-hour period and then for a 2-hour period immediately prior to the oral administration of Su-5879. The diuretic was given in an initial dosage of 300 mg. in the first 7 patients, and 200 mg. in the other 12 patients. Urines were then collected over 2-hour periods for the next 10 hours, measured, and analyzed for content of Na, K, and Cl. Then a 12-hour

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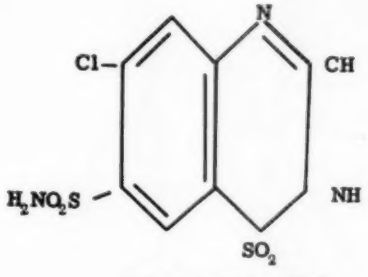
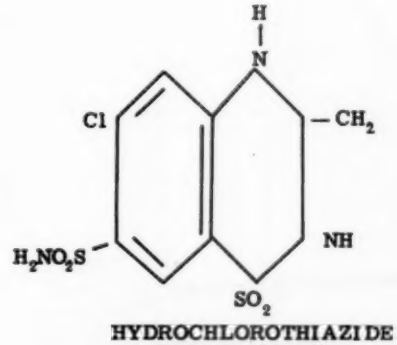
*Esidrix, brand of hydrochlorothiazide was supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.

specimen was similarly collected and analyzed, and thereafter 24-hour specimens. After 48 hours the patients were placed on a maintenance regimen of 50 mg. of Su-5879, three times daily in the 7 patients who had received the higher initial dose, and twice daily in the other 12 patients. The patients were followed clinically, and body weights were determined daily. Determinations of serum electrolytes and BUN were made at the end of the initial 48-hour period of study, and weekly thereafter. Follow-up blood counts, urinalyses, and venous pressures were determined weekly.

The outclinic patients were in less severe failure, and were evaluated once to twice weekly, but determinations of urinary volume and urinary electrolytes were not made. In these patients, Su-5879 therapy was initiated and continued at 50 mg. twice daily. Complete blood count, urinalysis, and determinations of BUN, serum Na, K, Cl, and CO_2 were made prior to the administration of the diuretic, at each clinic visit for the first several weeks, and each 2 to 3 weeks thereafter.



CHLOROTHIAZIDE



HYDROCHLOROTHIAZIDE
ESIDRIX (CIBA)
SU-5879

Fig. 1.—See text.

Su-5879 was also given in a dosage usually of 50 mg. twice daily to 13 ambulatory hypertensive patients not in congestive heart failure (Table IV). All of these patients were previously on antihypertensive therapy, most often Su-3118*, which had been moderately effective, but which had not achieved the desired reduction in blood pressure. Throughout the period of study, such supplementary medication was maintained at a level similar to that of the control period. Su-5879 was begun after a control period of 2 to 3 weeks, and the patients were clinically evaluated once to twice weekly. At each visit, blood pressures were taken after a rest period of 1 hour, usually with the patient in the sitting position. Determinations of BUN were made before Su-5879 was given, and again each 1 to 2 weeks throughout the period of study. Only occasionally were serum electrolytes determined in this group.

*Singoserp, brand of syrosingopine (Ciba).

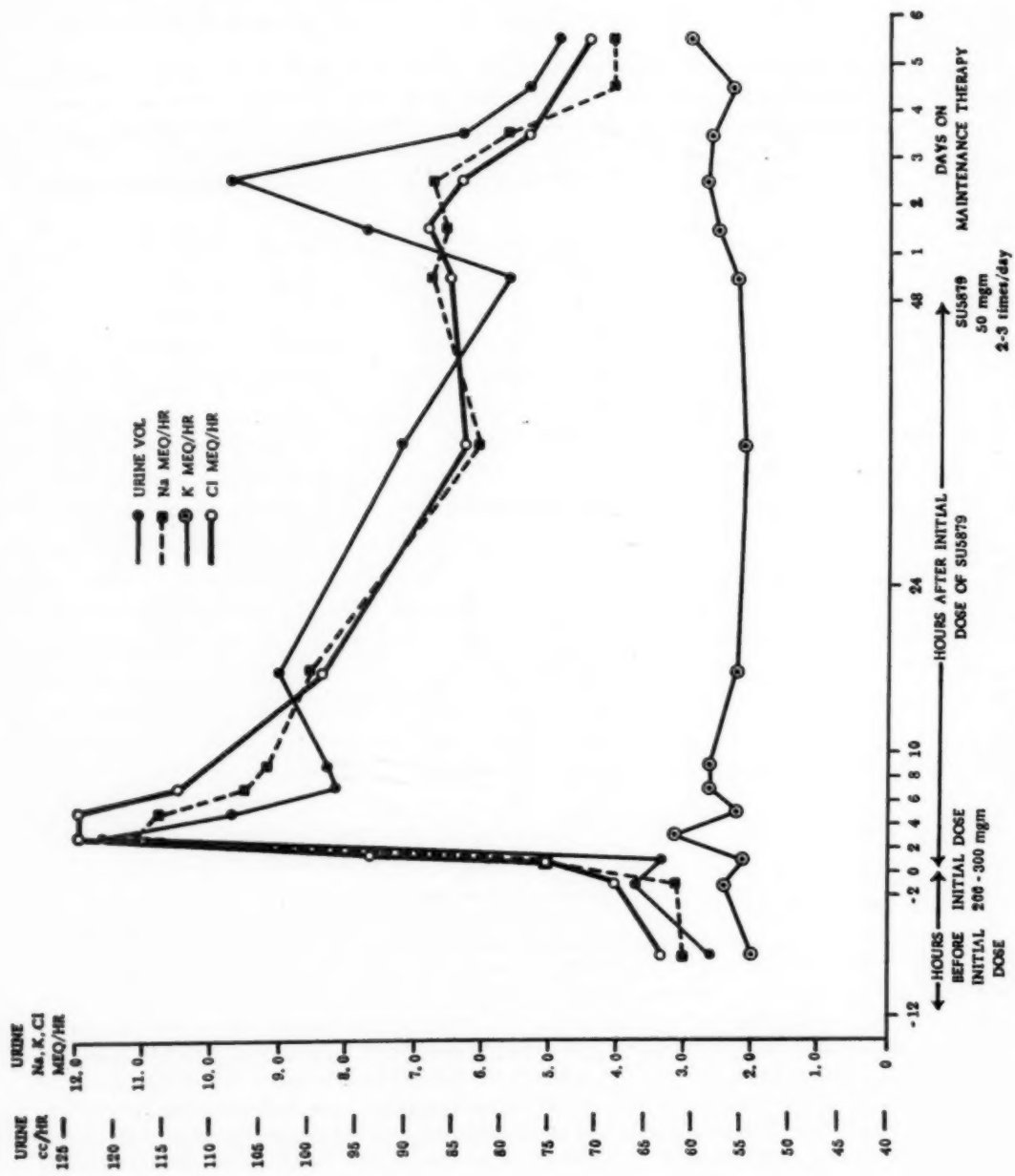


Fig. 2.—Effects of Su-5879 on volume of urine and electrolytes in 19 patients with congestive heart failure.

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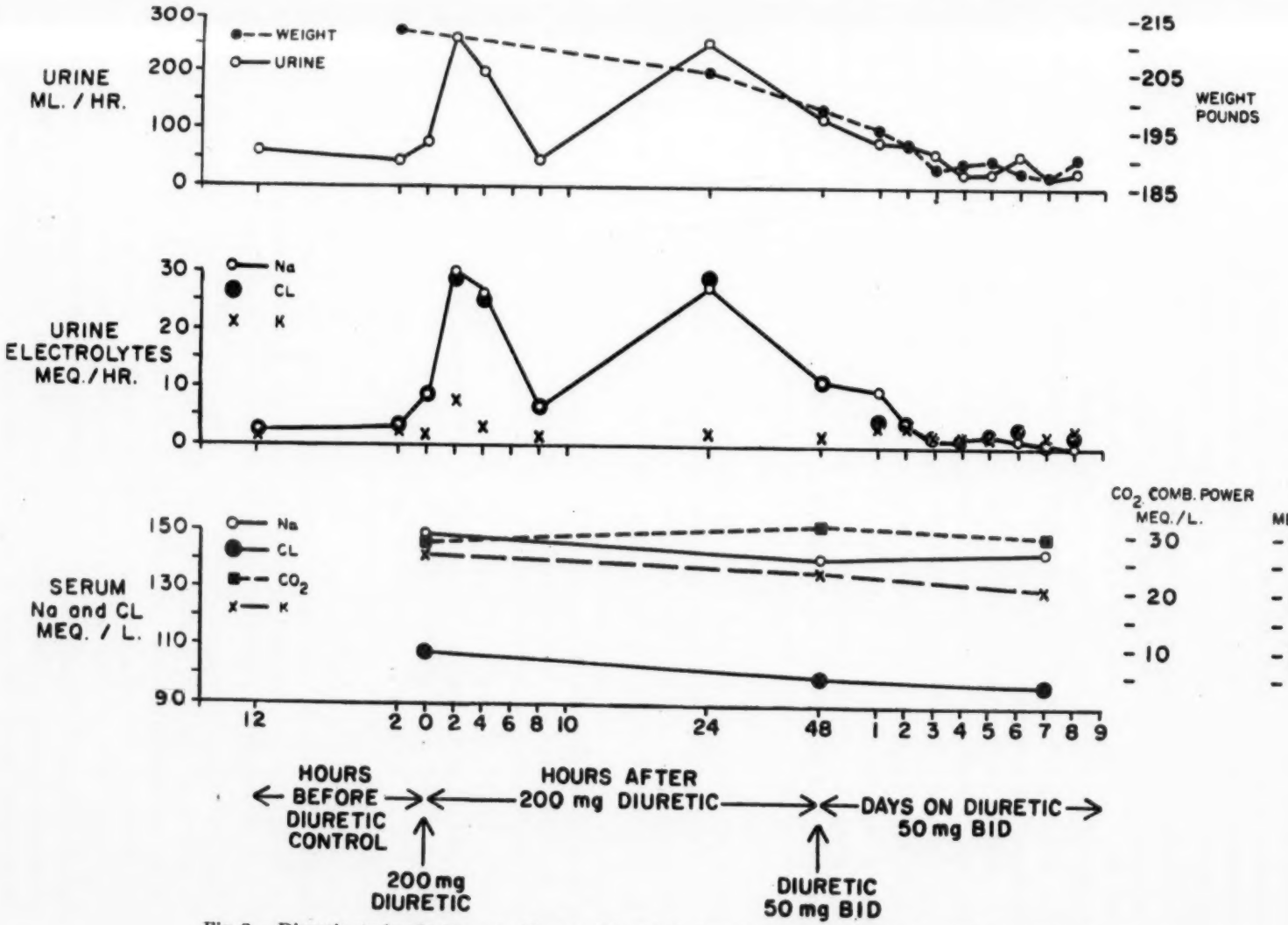

Fig. 3.—Diuretic study of a 62-year-old man with arteriosclerotic and hypertensive heart disease and failure.

RESULTS

Diuretic Results in Hospitalized Patients.—There were 19 hospitalized patients in congestive heart failure, with diagnoses of coronary heart disease in 11, hypertensive heart disease in 5, and rheumatic heart disease in 3. Venous pressures prior to the administration of the drug ranged from 15 to 31 cm. of saline, the average being 23.4 cm. Values of blood urea nitrogen initially were below 20 mg. per cent in all patients except 5; the elevated levels were 21, 23, 26 44, and 108 mg. per cent. The blood counts were within normal limits, except for a moderate anemia in the patient with the highest values of blood urea nitrogen, and depression of all marrow elements in a patient with myelofibrosis. Values of serum protein were normal.

Sixteen of the patients had a satisfactory diuresis clinically; the duration of diuresis, determined on the basis of daily weights and urinary outputs, was from 4 to 14 days. In the entire group of 19 patients the average loss of weight in the first 24 hours was 3.3 pounds (varying from 0 in the nonresponsive patients to a maximum of 8 pounds). The average loss of weight in the first week was 13.3 pounds (varying from 0 to a maximum of 34 pounds). Venous pressures returned to less than 15 cm. of saline in all except the 3 patients who did not have a diuresis. One patient had nausea and vomiting after taking the drug, but this seemed to be due definitely to the state of congestive failure, for she was given the drug without such symptoms after digitalization.

Three hospitalized patients failed to respond to Su-5879. One of these had complicating myelofibrosis, with anemia, and a borderline low serum albumin. Another had hypothyroidism, diabetes, and renal disease, with blood urea nitrogen elevated to 108 mg. per cent; the congestive failure in this patient was also unresponsive to all other measures. The remaining patient was a 70-year-old man with arteriosclerotic heart disease in whom Su-5879 did not produce a diuresis; he later became partially compensated on digitalization and mercaptomerin. The cause for unresponsiveness of this patient to Su-5879 was not determined. His initial blood urea nitrogen was 26 mg. per cent, and there were normal serum electrolytes and serum proteins.

Fig. 2 shows the average volume of urine (in c.c./hr.) and excretion (in mEq./hr.) of sodium, potassium, and chloride in the 19 hospitalized patients before and after the administration of Su-5879. The average urinary volume doubled in the second 2-hour period following the administration of 200 or 300 mg. of Su-5879, and continued at increased amounts for 48 hours, despite discontinuance of the drug until the end of that period. An abrupt secondary rise in urinary volume lasting 2 days occurred after the beginning of the maintenance dosage of 50 mg. two to three times daily. The average urinary volume stayed above the base-line value until the end of the thirteenth day, except for a drop on the ninth day, which we are unable to explain. The excretion of sodium increased by over 60 per cent in the first 2 hours, and then increased by over three times in the subsequent three 2-hour periods. It then gradually decreased to twice the control in the second 24-hour period. It remained well above initial levels throughout the first 8 days, but was below the control values from the eighth to the thirteenth day. Excretion of potassium increased to a maximum of

50 per cent above the control at the second 2-hour period following initial administration of the drug. Most of the subsequent determinations were somewhat elevated over the control, but were considerably less than the percentage augmentation of sodium. However, determinations from the fifth to the thirteenth days showed excretion of potassium to be at higher levels than initially (from 3.0 to 3.5 mEq./hr.), in contrast to the diminishing excretion of sodium at this time. The output of chloride was augmented in essentially the same manner as that of sodium throughout the entire period of study.

Table I summarizes the levels of serum electrolytes and CO_2 before and after the administration of Su-5879; the last column shows the number of days of diuretic therapy. Levels of serum sodium became abnormally low (120 and 125 mEq./liter) in 2 patients, but increased to normal in one patient in whom the control determination was low. The serum potassium decreased in 7 of 18 patients. It decreased to 4.0 mEq./liter in one patient after 6 days of therapy, to 3.8 mEq./liter in another after 11 days, and to 3.1 mEq./liter in another after 11 days. Levels of serum chloride decreased in all but 3 patients—to less than 95 mEq./liter in 3 patients (to 80 in one of these). Levels of serum CO_2 increased in 11 patients, but exceeded 30 mm./liter in only 2 patients. In a uremic patient (Case No. 17), levels of CO_2 increased from 10 to 16 mm./liter after 7 days of therapy.

TABLE I. SERUM ELECTROLYTES IN HOSPITALIZED PATIENTS

CASE NUMBER	BEFORE THERAPY				AFTER THERAPY				DAYS OF THERAPY
	NA	K (MEQ./L.)	CL	CO_2 (MM./L.)	NA	K (MEQ./L.)	CL	CO_2 (MM./L.)	
1.	130	6.1	94	19.7	120	7.3	80	23.5	28
2.	127	4.7	100	26.0	147	5.0	99	17.5	18
3.	143	4.4	102	25.2	135	5.7	91	21.0	14
4.	143	5.4	108	21.7	147	5.5	104	27.0	6
5.	141	4.4	112	21.0	149	4.9	108	34.0	22
6.	139	6.2	109	25.2	150	5.0	106	28.0	14
7.	150	5.1	107	21.0	140	4.2	97	28.2	17
8.	142	4.6	113	17.5	140	4.0	101	26.8	6
9.	147	4.3	101	18.6	152	3.1	96	29.4	11
10.	149	4.6	108	27.3	138	5.4	102	25.2	12
11.	141	4.7	108	24.4	147	4.9	108	30.7	9
12.	140	5.3	111	30.2	138	7.1	102	23.5	7
13.	150	5.3	105	32.4	138	5.7	96	26.5	14
14.	134	4.2	104	21.0	140	3.8	97	21.8	11
15.	144	5.6	96	23.1	140	4.4	101	28.1	28
16.	138	5.5	94	25.4	148	6.4	101	26.7	9
17.	136	5.0	115	10.0	125	6.8	112	16.0	7
18.	136	4.9	107	24.0	133	4.6	100	24.0	7

Urines were nearly always acid in reaction after the drug had been given, and there were no adverse changes in urinary protein or sediment. Blood counts showed no abnormal effect of the drug. Of the 5 patients who had an initial blood urea nitrogen of over 20 mg. per cent, 2 after 2 weeks of therapy showed

further elevations from 23 to 30 and from 26 to 40 mg. per cent. Four other patients showed rises in blood urea nitrogen after 2 weeks, from 18 to 30, 19 to 25, 11 to 23, and 18 to 24. Three patients with initial elevations of blood urea nitrogen showed reductions, from 108 to 100, 44 to 42, and 21 to 15.

Fig. 3 is a chart of the weight, urinary volume, urinary electrolyte excretion, and serum electrolyte and CO_2 values in a responsive patient.

Diuretic Results in Outclinic Patients.—The 20 outclinic patients with edema had less severe congestive heart failure than those patients in the hospital. Ten of these had coronary heart disease, 8 hypertensive heart disease, and 2 rheumatic heart disease. All of these had satisfactory diuresis, except one patient with minimal edema due to arteriosclerotic heart disease. There was an average loss of weight of 3.6 pounds in the first week, and 3.6 pounds in the second week. Eleven of these patients were treated with Su-5879 for a period exceeding 4 weeks, and 7 for a period exceeding 8 weeks. One patient developed nausea and vomiting when given Su-5879.

TABLE II. SERUM ELECTROLYTES IN OUTCLINIC PATIENTS

CASE NUMBER	BEFORE THERAPY				AFTER THERAPY				DAYS OF THERAPY
	NA	K (MEQ./L.)	CL	CO_2 (MM./L.)	NA	K (MEQ./L.)	CL	CO_2 (MM./L.)	
1.	152	4.9	109	26.0	143	4.5	98	32.8	3
2.	146	6.1	113	26.5	146	5.1	104	36.1	1
3.	147	4.1	100	21.0	148	4.6	108	29.0	2
4.	146	3.5	109	28.0	152	4.6	96	36.1	2
5.	144	4.3	101	28.7	146	4.3	98	30.2	2
6.	140	3.8	108	28.2	143	5.0	95	30.0	1
7.	152	4.9	109	26.0	147	5.2	98	29.0	9
8.	138	7.1	102	24.0	141	4.9	101	29.4	6
9.	149	5.9	115	26.0	137	5.2	104	26.0	3
10.	159	5.2	121	28.0	140	3.4	97	31.0	3
11.	138	3.9	98	32.4	142	5.2	95	30.2	3
12.	147	5.0	108	26.0	138	3.6	95	25.0	2
13.	143	5.7	——	——	140	4.7	97	25.7	5
14.	141	4.1	103	24.0	137	3.7	99	19.0	2
15.	147	4.4	110	24.0	152	4.6	112	25.0	8
16.	147	4.3	102	24.6	151	3.5	106	26.0	4
17.	140	4.4	105	25.0	137	3.0	94	25.0	2
18.	146	4.2	110	25.0	139	4.0	106	24.0	2
19.	148	4.1	106	22.0	154	3.7	107	26.5	3

The levels of serum electrolytes and CO_2 in this group of patients are summarized in Table II. Six of 19 patients had levels of serum potassium below 4.0 mEq./liter after therapy of from 2 to 6 weeks. However, only one patient, with serum potassium of 3.4 mEq./liter, had clinical symptoms of hypopotassemia, with marked weakness. In 2 patients the initial levels of potassium of 3.5 and 3.8 mEq./liter rose to within normal levels after treatment. Values of serum sodium and chloride remained within normal limits. The final values of CO_2 exceeded 35 mm./liter in 2 patients.

Initial values of blood urea nitrogen exceeded 20 mg. in 4 patients, being 24, 27, 32, and 41 mg. per cent. This determination rose from 41 to 44 in one patient after 8 weeks of therapy; from 21 to 28 in another in 4 weeks; from 32 to 40 in 2 weeks, and from 25 to 35 in 5 weeks. In 4 other patients the initial values of blood urea nitrogen of 19, 19, 18, and 16 mg. per cent rose, respectively, to 21 in 2 weeks, to 25 in 5 weeks, to 21 in 3 weeks, and to 24 in 4 weeks. Urinalyses and blood counts following the administration of Su-5879 to these patients showed no adverse changes.

Effects of Su-5879 on Blood Pressure in Hypertensive Patients.—The etiology of the heart disease in 13 of the hospitalized and ambulatory patients discussed previously was essential hypertension. Table III lists the blood pressures before and after the administration of Su-5879, which in these patients was given primarily to evaluate diuretic effects. Three of the patients had been maintained on Su-3118 (syrosingopine, Ciba) for at least 4 weeks prior to receiving Su-5879, and the former was continued at the same dosage throughout the study. The other patients had no additional antihypertensive medication.

TABLE III. EFFECTS ON BLOOD PRESSURE OF SU-5879 IN HYPERTENSIVE PATIENTS IN CONGESTIVE HEART FAILURE

PATIENT	OTHER DRUGS	DAILY DOSAGE (MG.)	CONTROL B.P. (MM. Hg)	FINAL B.P. (MM. Hg)	CHANGE IN MEAN B.P.	WEEKS OF THERAPY
L. B.	None	150	150/90	120/80	−17	2
T. J.	None	100	190/100	220/120	+17	2
M. H.	None	100	160/92	158/90	− 2	3
I. W.	Su-3118	100	174/130	148/113	−17	5
H. K.	None	100	150/98	115/68	−32	11
C. D.	None	100	190/92	170/90	− 8	11
B. E.	Su-3118	150	150/90	220/130	+50	2
C. A.	Su-3118	150	190/100	174/108	0	3
S. S.	None	100	190/110	136/80	−38	11
O. G.	None	100	148/100	110/70	−33	7
O. L.	None	100	170/98	184/80	− 8	3
S. H.	None	100	138/106	132/80	−13	3
F. D.	None	100	152/100	140/80	−17	1

There was a decrease in mean blood pressure (diastolic pressure plus one third pulse pressure) of more than 20 mm. Hg in 3 patients. However, in 6 additional patients the diastolic pressure following therapy with Su-5879 was 90 mm. Hg or less. Thus, 9 of the 13 patients were regarded to have had a significant decrease in blood pressure after being given Su-5879. A drop in blood pressure due to the failure state may explain the conspicuous rise following circulatory compensation in 2 patients (T.J. and B.E.).

Table IV summarizes the effects of Su-5879 in 13 ambulatory hypertensive patients who were not in congestive heart failure. All of these had essential hypertension except 2 (H.M. and G.Y.); these 2 had primary renal disease. The simultaneously administered antihypertensive drugs, which are listed in

the table, had been given for at least 3 weeks prior to beginning the use of Su-5879, and were continued at the same dosage throughout the study. No patients had elevated levels of blood urea nitrogen.

TABLE IV. EFFECTS ON BLOOD PRESSURE OF SU-5879 IN HYPERTENSIVE PATIENTS NOT IN CONGESTIVE FAILURE

PATIENT	OTHER DRUGS	DAILY DOSAGE (MG.)	CONTROL B.P. (MM. Hg)	FINAL B.P. (MM. Hg)	CHANGE IN MEAN B.P.	WEEKS OF THERAPY
L. B.	Su-3118	100	190/110	150/92	−25	9
S. J.	Su-3118	150	176/104	156/100	− 9	4
H. P.	Rauwolfia Apresoline	100	200/110	168/98	−19	4
T. M.	Su-3118	100	175/116	140/90	−29	2
C. P.	Su-3118	100	186/124	150/98	−29	6
J. B.	Reserpine	100	226/126	140/98	−47	3
W. J.	Su-3118	100	186/110	154/94	−21	5
H. M.	Su-3118	100	210/120	210/116	− 3	2
G. Y.	Su-3118	100	220/130	210/120	−10	4
M. C.	Su-3118	100	216/126	145/100	−41	2
M. T.	Su-3118 Ansolysen	100	214/134	160/90	−47	3
M. F.	Su-3118	100	230/130	170/94	−51	7
T. B.	Su-3118	50	198/130	150/90	−43	5

In this group, Su-5879 at a dosage usually of 50 mg. twice daily resulted in a fall in mean blood pressure of 20 mm. Hg or more in 9 patients. The fall occurred within the first 1 to 2 weeks, and was maintained throughout the period of therapy. In 3 patients the diastolic pressure was decreased to 90 mm. Hg. Although all of the patients showed a decrease in blood pressure, the 2 with primary renal disease showed a relatively poor response. Levels of blood urea nitrogen remained within normal limits.

DISCUSSION

Su-5879 appears to be a clinically effective oral diuretic which is well tolerated. The initial oral doses of 300 mg. for hospitalized patients, and maintenance doses of 50 mg. three times daily, were apparently higher than necessary in most cases. The later regimen of 200 mg. for initial action and 50 mg. twice daily for maintenance was just as effective in our patients.

The diuretic effect appears to be similar to that of the mercurials and chlorothiazide, in that urinary volume is augmented, with predominantly an excretion of sodium and chloride to about 3 times the control levels. Excretion of potassium was increased to a maximum of 50 per cent above the control, but during the second week of observation it increased slightly above this level, while the excretion of sodium diminished. Levels of serum potassium below 4.0 mEq./liter were observed in only 2 patients during short-term hospital therapy. However, in the outclinic group, 6 of 19 patients developed levels of potassium below 4.0 mEq./liter after therapy of from 2 to 6 weeks. One outclinic patient developed

clinical symptoms of hypopotassemia, and this patient became asymptomatic upon the discontinuance of Su-5879 and the administration of oral potassium.

Although none of our patients developed serious renal insufficiency, the rise in the values of blood urea nitrogen observed in some indicate a need for caution in the administration of this drug. Two hospitalized patients with slight initial elevations of blood urea nitrogen and 3 others with initially normal values showed a moderate rise after short-term therapy. However, 3 other hospitalized patients with initial elevations of blood urea nitrogen showed a decrease after treatment. In the ambulatory patients with edema, 4 with slight elevations of blood urea nitrogen and 4 others with initially normal values showed slight rises after several weeks of therapy. No serious uremic complications occurred, and urinalyses in these showed no adverse changes.

Determinations of blood pressure before and after the administration of Su-5879 to patients with hypertension demonstrate a significant fall in 18 of 26 patients. The decrease in pressure was most dramatic in the patients not in congestive heart failure, but these as a group had a higher initial pressure than the patients in failure. Since most of the nonfailure patients were receiving Su-3118 (syrosingopine, Ciba) before and throughout the study, the more dramatic reductions in blood pressure in this group may have resulted from the potentiating effects of this reserpine derivative. None of the compensated hypertensive patients had significant adverse effects of blood urea nitrogen after therapy with Su-5879.

SUMMARY

1. Su-5879 (hydrochlorothiazide, Ciba) has been demonstrated to be an effective diuretic of low toxicity in studies on 19 hospitalized and 17 outclinic patients in congestive heart failure.

2. The diuretic effect is similar to that of the mercurials and chlorothiazide, in that there results mainly an outpouring of sodium and chloride, with a decrease in the levels of chloride and an increase of CO_2 in the serum.

3. A single dose of 200 mg. produces a conspicuous diuresis within about 2 hours after ingestion, and this is maintained for over 24 hours. Effective diuresis can also be achieved by doses of 50 mg. administered twice daily.

4. Excretion of potassium was increased moderately, and in a few patients levels of serum potassium below 4.0 mEq./liter appeared after 1 week of therapy. However, only one patient in our series had clinical symptoms of hypopotassemia.

5. Slight elevations in blood urea nitrogen after therapy were observed in some of our patients in congestive heart failure. None developed serious renal insufficiency. If oliguria develops and the blood urea nitrogen rises under treatment, the drug should be withdrawn.

6. Significant reductions in blood pressure occurred in 18 of 26 hypertensive patients. The antihypertensive action of Su-5879 appears most promising.

7. Su-5879 produced no serious complications in our cases. However, the resulting low values for serum potassium in a few of our patients, and the occasional moderate rises in values of blood urea nitrogen would, as with chlorothiazide, call for caution in long-term therapy.

3. *Diuretic and Biochemical Effects Associated With Daily Administration of Flumethiazide.*—There was a continuing excretion of sodium following daily therapy with flumethiazide until the body stores were depleted. (These patients were eating a diet containing only 50 mEq. of sodium per day.) A very minimal rise in blood urea nitrogen was observed. There was a tendency to slight elevation of the carbon-dioxide combining power, but this was moderate and not clinically significant. Changes in sodium, potassium, and chloride were not significant (Fig. 5).

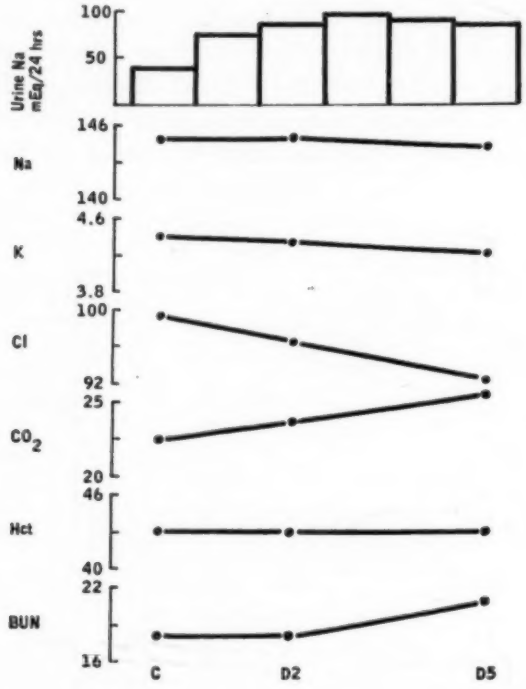

Fig. 5.—Diuretic and biochemical effects associated with the daily administration of flumethiazide (1.0 Gm. daily for 5 consecutive days). There is a continuing response in the excretion of sodium until the body stores are depleted. There is a tendency toward the development of hypochloremic alkalosis.

DISCUSSION

Flumethiazide (Ademol) is an interesting compound in that it differs structurally from chlorothiazide only by the presence of a trifluoromethyl group in the place of chloride. In spite of this shift in a radical there is no significant pharmacologic difference between the two compounds, based upon the results of the current study. Both drugs are of extreme value as diuretic agents because (1) they can be administered orally, (2) they are repetitively effective (that is, tolerance does not develop), and (3) they are virtually free of acute toxicity. The changes in biochemical architecture following the administration of this drug is similar to those following the administration of chlorothiazide; there is a tendency toward hypochloremic alkalosis. While the potency estimation of flumethiazide is 0.7, the potency estimation of chlorothiazide is 0.8. That is

they are 70 and 80 per cent, respectively, as potent as meralluride (Mercuhydrin) parenterally administered. Subjecting these data to a simple Student's "t" test revealed no significant difference between the natriuretic potency of the two orally effective compounds.

A more critical evaluation of the electrolyte and urinary volume relationships of these two compounds suggests that flumethiazide may have a greater effect on the excretion of water than does chlorothiazide. Expressed in another way, it is suggested that in doses producing equivalent diuresis (increase of water), the excretion of sodium is only 70 per cent as great.

Thus, the basic clinical pharmacologic studies of flumethiazide in human beings suggest that this drug may be of extreme value in the treatment of various states of edema,[2] and, perhaps, as an adjunct in antihypertensive therapy.[3]

TABLE I. DIURETIC RESPONSES TO SINGLE DOSES OF FLUMETHIAZIDE

	AVERAGES OF DETERMINATIONS ON 10 PATIENTS							
	1.0 GM. DOSE				2.0 GM. DOSE			
	C	D	I	P VALUE*	C	D	I	P VALUE
Urine Volume (L./24 hr.)	3.0	3.3	0.3	.01	3.0	3.5	0.5	.01
Urine Sodium (mEq./24 hr.)	45	85	40	.001	45	135	90	.001
Body Weight (Kg.)	65	64.6	−0.4	.01	65	64.2	−0.8	.01

*P value: Determined from Student's "t" test.
C: Control. D: Drug. I: Increase.

CONCLUSIONS

Flumethiazide has been subjected to study by clinical pharmacologic techniques, with attention to its action as a diuretic agent. The results revealed that it is not significantly different from chlorothiazide in its diuretic potency or in its ability to produce changes in biochemical architecture. Furthermore, the drug is repetitively effective on daily use. The initial data, therefore, suggest that flumethiazide is of potential value in the long-term management of various states of edema, and, perhaps, as an adjunct in the therapy of hypertension.

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The Effects of SU-5879 (Esidrix*) in Congestive Heart Failure and Hypertension: A Clinical Evaluation

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The most significant recent advance in the therapy of edema has been the introduction and use of the newly developed sulfonamide derivatives. The first of these was acetazoleamide,[1,2] which produces diuresis by the inhibition of carbonic anhydrase. More effective diuretic action results from chlorothiazide,[3,4] which also inhibits carbonic anhydrase, but augments urinary output in a manner similar to the mercurials. Furthermore, chlorothiazide has been shown to be of considerable value as an antihypertensive agent.[5]

Su-5879 (Ciba), or hydrochlorothiazide, was synthesized in the search for new and possibly more effective diuretic and antihypertensive drugs in the sulfonamide group. It is closely related to chlorothiazide, as shown in Fig. 1. Preliminary experiments[6] showed Su-5879 to be from 7 to 16 times as active as chlorothiazide in producing diuresis in the dog and rat, although only one ninth as potent in its capacity to inhibit carbonic anhydrase. It also appeared to have a longer duration of diuretic action in equipotent dosage, and less potassium dissipating effect.

METHOD OF STUDY

We have determined the effects of Su-5879 on the electrolyte patterns in the urine and plasma during clinical diuresis in 19 hospitalized and 20 outclinic patients with edema due to congestive heart failure. Each of our inpatients was begun with a control period of 3 to 4 days, during which the regimen of therapy for the congestive heart failure was kept constant, a low-sodium diet (500 mg.) was administered, and all other diuretic agents and potassium were withheld. During this period there was careful clinical evaluation, with complete blood count, urinalysis, and determination of daily body weight, venous pressure, blood urea nitrogen (BUN), and serum Na, K, Cl, and CO_2. Specimens of urine were collected and measured, and the content of Na, K, and Cl was determined for a 12-hour period and then for a 2-hour period immediately prior to the oral administration of Su-5879. The diuretic was given in an initial dosage of 300 mg. in the first 7 patients, and 200 mg. in the other 12 patients. Urines were then collected over 2-hour periods for the next 10 hours, measured, and analyzed for content of Na, K, and Cl. Then a 12-hour

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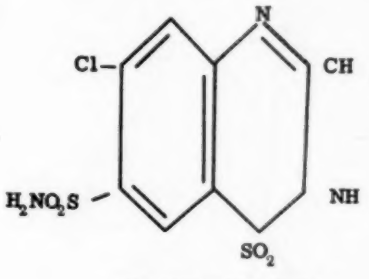
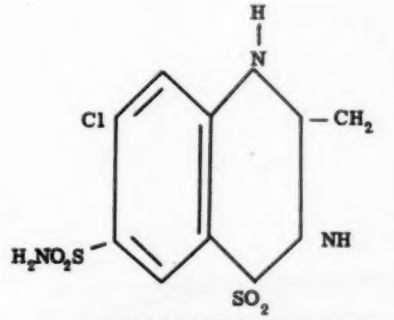
*Esidrix, brand of hydrochlorothiazide was supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.

specimen was similarly collected and analyzed, and thereafter 24-hour specimens. After 48 hours the patients were placed on a maintenance regimen of 50 mg. of Su-5879, three times daily in the 7 patients who had received the higher initial dose, and twice daily in the other 12 patients. The patients were followed clinically, and body weights were determined daily. Determinations of serum electrolytes and BUN were made at the end of the initial 48-hour period of study, and weekly thereafter. Follow-up blood counts, urinalyses, and venous pressures were determined weekly.

The outclinic patients were in less severe failure, and were evaluated once to twice weekly, but determinations of urinary volume and urinary electrolytes were not made. In these patients, Su-5879 therapy was initiated and continued at 50 mg. twice daily. Complete blood count, urinalysis, and determinations of BUN, serum Na, K, Cl, and CO_2 were made prior to the administration of the diuretic, at each clinic visit for the first several weeks, and each 2 to 3 weeks thereafter.



CHLOROTHIAZIDE



HYDROCHLOROTHIAZIDE
ESIDRIX (CIBA)
SU-5879

Fig. 1.—See text.

Su-5879 was also given in a dosage usually of 50 mg. twice daily to 13 ambulatory hypertensive patients not in congestive heart failure (Table IV). All of these patients were previously on antihypertensive therapy, most often Su-3118*, which had been moderately effective, but which had not achieved the desired reduction in blood pressure. Throughout the period of study, such supplementary medication was maintained at a level similar to that of the control period. Su-5879 was begun after a control period of 2 to 3 weeks, and the patients were clinically evaluated once to twice weekly. At each visit, blood pressures were taken after a rest period of 1 hour, usually with the patient in the sitting position. Determinations of BUN were made before Su-5879 was given, and again each 1 to 2 weeks throughout the period of study. Only occasionally were serum electrolytes determined in this group.

*Singoserp, brand of syrosingopine (Ciba).

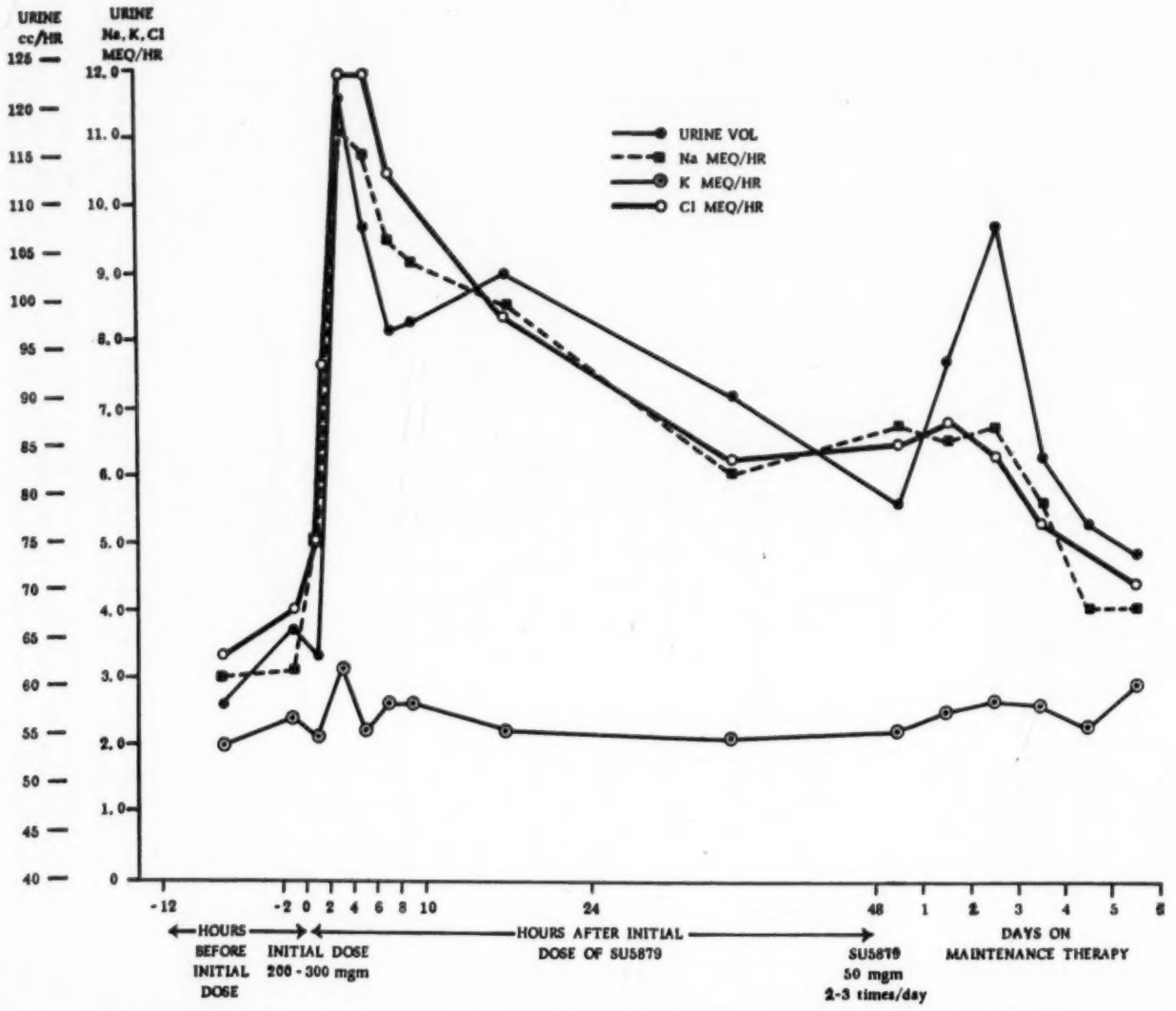


Fig. 2.—Effects of Su-5879 on volume of urine and electrolytes in 19 patients with congestive heart failure.

300 WEIGHT

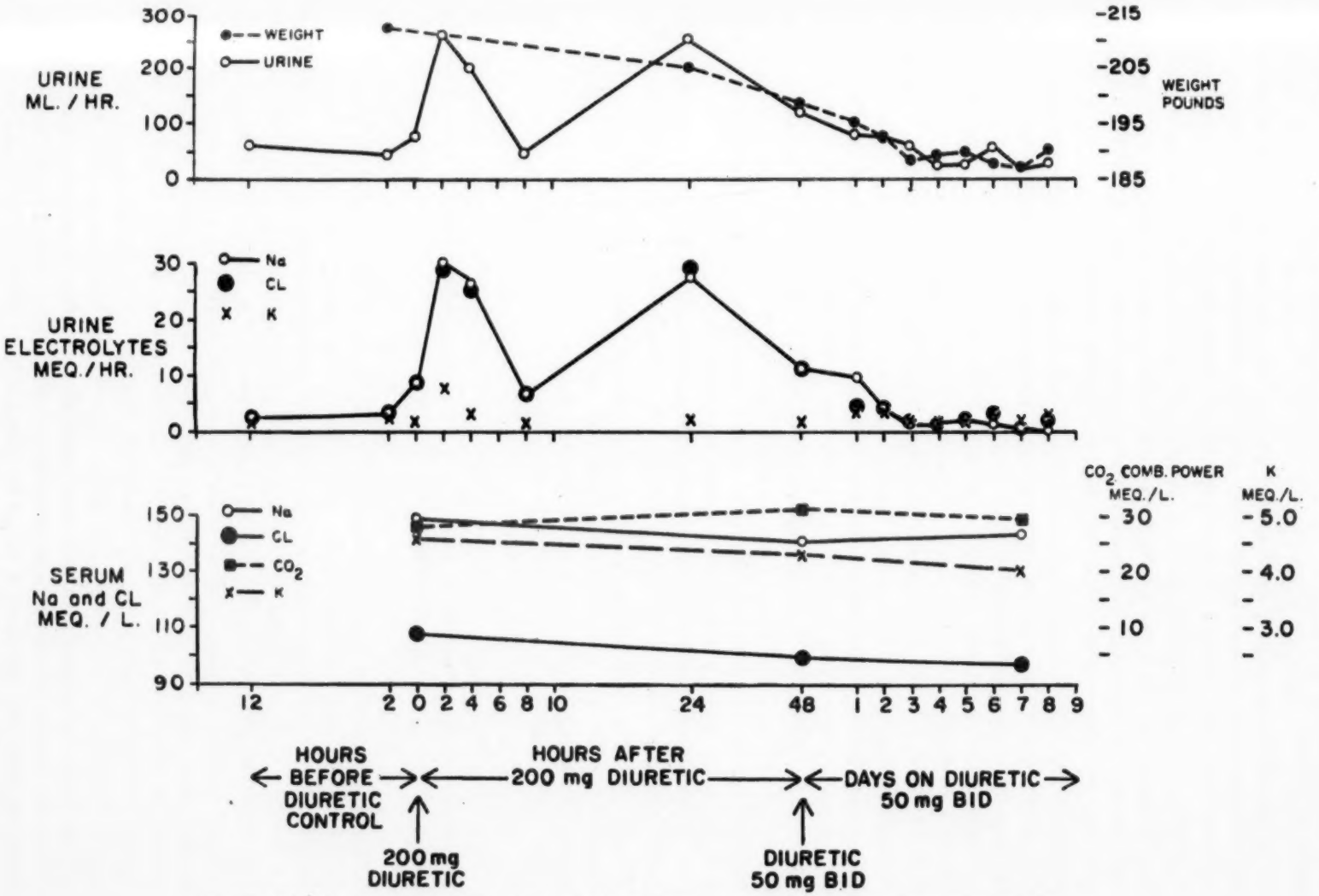


Fig. 3.—Diuretic study of a 62-year-old man with arteriosclerotic and hypertensive heart disease and failure.

RESULTS

Diuretic Results in Hospitalized Patients.—There were 19 hospitalized patients in congestive heart failure, with diagnoses of coronary heart disease in 11, hypertensive heart disease in 5, and rheumatic heart disease in 3. Venous pressures prior to the administration of the drug ranged from 15 to 31 cm. of saline, the average being 23.4 cm. Values of blood urea nitrogen initially were below 20 mg. per cent in all patients except 5; the elevated levels were 21, 23, 26 44, and 108 mg. per cent. The blood counts were within normal limits, except for a moderate anemia in the patient with the highest values of blood urea nitrogen, and depression of all marrow elements in a patient with myelofibrosis. Values of serum protein were normal.

Sixteen of the patients had a satisfactory diuresis clinically; the duration of diuresis, determined on the basis of daily weights and urinary outputs, was from 4 to 14 days. In the entire group of 19 patients the average loss of weight in the first 24 hours was 3.3 pounds (varying from 0 in the nonresponsive patients to a maximum of 8 pounds). The average loss of weight in the first week was 13.3 pounds (varying from 0 to a maximum of 34 pounds). Venous pressures returned to less than 15 cm. of saline in all except the 3 patients who did not have a diuresis. One patient had nausea and vomiting after taking the drug, but this seemed to be due definitely to the state of congestive failure, for she was given the drug without such symptoms after digitalization.

Three hospitalized patients failed to respond to Su-5879. One of these had complicating myelofibrosis, with anemia, and a borderline low serum albumin. Another had hypothyroidism, diabetes, and renal disease, with blood urea nitrogen elevated to 108 mg. per cent; the congestive failure in this patient was also unresponsive to all other measures. The remaining patient was a 70-year-old man with arteriosclerotic heart disease in whom Su-5879 did not produce a diuresis; he later became partially compensated on digitalization and mercaptomerin. The cause for unresponsiveness of this patient to Su-5879 was not determined. His initial blood urea nitrogen was 26 mg. per cent, and there were normal serum electrolytes and serum proteins.

Fig. 2 shows the average volume of urine (in c.c./hr.) and excretion (in mEq./hr.) of sodium, potassium, and chloride in the 19 hospitalized patients before and after the administration of Su-5879. The average urinary volume doubled in the second 2-hour period following the administration of 200 or 300 mg. of Su-5879, and continued at increased amounts for 48 hours, despite discontinuance of the drug until the end of that period. An abrupt secondary rise in urinary volume lasting 2 days occurred after the beginning of the maintenance dosage of 50 mg. two to three times daily. The average urinary volume stayed above the base-line value until the end of the thirteenth day, except for a drop on the ninth day, which we are unable to explain. The excretion of sodium increased by over 60 per cent in the first 2 hours, and then increased by over three times in the subsequent three 2-hour periods. It then gradually decreased to twice the control in the second 24-hour period. It remained well above initial levels throughout the first 8 days, but was below the control values from the eighth to the thirteenth day. Excretion of potassium increased to a maximum of

50 per cent above the control at the second 2-hour period following initial administration of the drug. Most of the subsequent determinations were somewhat elevated over the control, but were considerably less than the percentage augmentation of sodium. However, determinations from the fifth to the thirteenth days showed excretion of potassium to be at higher levels than initially (from 3.0 to 3.5 mEq./hr.), in contrast to the diminishing excretion of sodium at this time. The output of chloride was augmented in essentially the same manner as that of sodium throughout the entire period of study.

Table I summarizes the levels of serum electrolytes and CO_2 before and after the administration of Su-5879; the last column shows the number of days of diuretic therapy. Levels of serum sodium became abnormally low (120 and 125 mEq./liter) in 2 patients, but increased to normal in one patient in whom the control determination was low. The serum potassium decreased in 7 of 18 patients. It decreased to 4.0 mEq./liter in one patient after 6 days of therapy, to 3.8 mEq./liter in another after 11 days, and to 3.1 mEq./liter in another after 11 days. Levels of serum chloride decreased in all but 3 patients—to less than 95 mEq./liter in 3 patients (to 80 in one of these). Levels of serum CO_2 increased in 11 patients, but exceeded 30 mm./liter in only 2 patients. In a uremic patient (Case No. 17), levels of CO_2 increased from 10 to 16 mm./liter after 7 days of therapy.

TABLE I. SERUM ELECTROLYTES IN HOSPITALIZED PATIENTS

CASE NUMBER	BEFORE THERAPY				AFTER THERAPY				DAYS OF THERAPY
	NA	K (MEQ./L.)	CL	CO_2 (MM./L.)	NA	K (MEQ./L.)	CL	CO_2 (MM./L.)	
1.	130	6.1	94	19.7	120	7.3	80	23.5	28
2.	127	4.7	100	26.0	147	5.0	99	17.5	18
3.	143	4.4	102	25.2	135	5.7	91	21.0	14
4.	143	5.4	108	21.7	147	5.5	104	27.0	6
5.	141	4.4	112	21.0	149	4.9	108	34.0	22
6.	139	6.2	109	25.2	150	5.0	106	28.0	14
7.	150	5.1	107	21.0	140	4.2	97	28.2	17
8.	142	4.6	113	17.5	140	4.0	101	26.8	6
9.	147	4.3	101	18.6	152	3.1	96	29.4	11
10.	149	4.6	108	27.3	138	5.4	102	25.2	12
11.	141	4.7	108	24.4	147	4.9	108	30.7	9
12.	140	5.3	111	30.2	138	7.1	102	23.5	7
13.	150	5.3	105	32.4	138	5.7	96	26.5	14
14.	134	4.2	104	21.0	140	3.8	97	21.8	11
15.	144	5.6	96	23.1	140	4.4	101	28.1	28
16.	138	5.5	94	25.4	148	6.4	101	26.7	9
17.	136	5.0	115	10.0	125	6.8	112	16.0	7
18.	136	4.9	107	24.0	133	4.6	100	24.0	7

Urines were nearly always acid in reaction after the drug had been given, and there were no adverse changes in urinary protein or sediment. Blood counts showed no abnormal effect of the drug. Of the 5 patients who had an initial blood urea nitrogen of over 20 mg. per cent, 2 after 2 weeks of therapy showed

further elevations from 23 to 30 and from 26 to 40 mg. per cent. Four other patients showed rises in blood urea nitrogen after 2 weeks, from 18 to 30, 19 to 25, 11 to 23, and 18 to 24. Three patients with initial elevations of blood urea nitrogen showed reductions, from 108 to 100, 44 to 42, and 21 to 15.

Fig. 3 is a chart of the weight, urinary volume, urinary electrolyte excretion, and serum electrolyte and CO_2 values in a responsive patient.

Diuretic Results in Outclinic Patients.—The 20 outclinic patients with edema had less severe congestive heart failure than those patients in the hospital. Ten of these had coronary heart disease, 8 hypertensive heart disease, and 2 rheumatic heart disease. All of these had satisfactory diuresis, except one patient with minimal edema due to arteriosclerotic heart disease. There was an average loss of weight of 3.6 pounds in the first week, and 3.6 pounds in the second week. Eleven of these patients were treated with Su-5879 for a period exceeding 4 weeks, and 7 for a period exceeding 8 weeks. One patient developed nausea and vomiting when given Su-5879.

TABLE II. SERUM ELECTROLYTES IN OUTCLINIC PATIENTS

CASE NUMBER	BEFORE THERAPY				AFTER THERAPY				DAYS OF THERAPY
	NA	K (MEQ./L.)	CL	CO_2 (MM./L.)	NA	K (MEQ./L.)	CL	CO_2 (MM./L.)	
1.	152	4.9	109	26.0	143	4.5	98	32.8	3
2.	146	6.1	113	26.5	146	5.1	104	36.1	1
3.	147	4.1	100	21.0	148	4.6	108	29.0	2
4.	146	3.5	109	28.0	152	4.6	96	36.1	2
5.	144	4.3	101	28.7	146	4.3	98	30.2	2
6.	140	3.8	108	28.2	143	5.0	95	30.0	1
7.	152	4.9	109	26.0	147	5.2	98	29.0	9
8.	138	7.1	102	24.0	141	4.9	101	29.4	6
9.	149	5.9	115	26.0	137	5.2	104	26.0	3
10.	159	5.2	121	28.0	140	3.4	97	31.0	3
11.	138	3.9	98	32.4	142	5.2	95	30.2	3
12.	147	5.0	108	26.0	138	3.6	95	25.0	2
13.	143	5.7	——	——	140	4.7	97	25.7	5
14.	141	4.1	103	24.0	137	3.7	99	19.0	2
15.	147	4.4	110	24.0	152	4.6	112	25.0	8
16.	147	4.3	102	24.6	151	3.5	106	26.0	4
17.	140	4.4	105	25.0	137	3.0	94	25.0	2
18.	146	4.2	110	25.0	139	4.0	106	24.0	2
19.	148	4.1	106	22.0	154	3.7	107	26.5	3

The levels of serum electrolytes and CO_2 in this group of patients are summarized in Table II. Six of 19 patients had levels of serum potassium below 4.0 mEq./liter after therapy of from 2 to 6 weeks. However, only one patient, with serum potassium of 3.4 mEq./liter, had clinical symptoms of hypopotassemia, with marked weakness. In 2 patients the initial levels of potassium of 3.5 and 3.8 mEq./liter rose to within normal levels after treatment. Values of serum sodium and chloride remained within normal limits. The final values of CO_2 exceeded 35 mm./liter in 2 patients.

Initial values of blood urea nitrogen exceeded 20 mg. in 4 patients, being 24, 27, 32, and 41 mg. per cent. This determination rose from 41 to 44 in one patient after 8 weeks of therapy; from 21 to 28 in another in 4 weeks; from 32 to 40 in 2 weeks, and from 25 to 35 in 5 weeks. In 4 other patients the initial values of blood urea nitrogen of 19, 19, 18, and 16 mg. per cent rose, respectively, to 21 in 2 weeks, to 25 in 5 weeks, to 21 in 3 weeks, and to 24 in 4 weeks. Urinalyses and blood counts following the administration of Su-5879 to these patients showed no adverse changes.

Effects of Su-5879 on Blood Pressure in Hypertensive Patients.—The etiology of the heart disease in 13 of the hospitalized and ambulatory patients discussed previously was essential hypertension. Table III lists the blood pressures before and after the administration of Su-5879, which in these patients was given primarily to evaluate diuretic effects. Three of the patients had been maintained on Su-3118 (syrosingopine, Ciba) for at least 4 weeks prior to receiving Su-5879, and the former was continued at the same dosage throughout the study. The other patients had no additional antihypertensive medication.

TABLE III. EFFECTS ON BLOOD PRESSURE OF SU-5879 IN HYPERTENSIVE PATIENTS IN CONGESTIVE HEART FAILURE

PATIENT	OTHER DRUGS	DAILY DOSAGE (MG.)	CONTROL B.P. (MM. Hg)	FINAL B.P. (MM. Hg)	CHANGE IN MEAN B.P.	WEEKS OF THERAPY
L. B.	None	150	150/90	120/80	−17	2
T. J.	None	100	190/100	220/120	+17	2
M. H.	None	100	160/92	158/90	− 2	3
I. W.	Su-3118	100	174/130	148/113	−17	5
H. K.	None	100	150/98	115/68	−32	11
C. D.	None	100	190/92	170/90	− 8	11
B. E.	Su-3118	150	150/90	220/130	+50	2
C. A.	Su-3118	150	190/100	174/108	0	3
S. S.	None	100	190/110	136/80	−38	11
O. G.	None	100	148/100	110/70	−33	7
O. L.	None	100	170/98	184/80	− 8	3
S. H.	None	100	138/106	132/80	−13	3
F. D.	None	100	152/100	140/80	−17	1

There was a decrease in mean blood pressure (diastolic pressure plus one third pulse pressure) of more than 20 mm. Hg in 3 patients. However, in 6 additional patients the diastolic pressure following therapy with Su-5879 was 90 mm. Hg or less. Thus, 9 of the 13 patients were regarded to have had a significant decrease in blood pressure after being given Su-5879. A drop in blood pressure due to the failure state may explain the conspicuous rise following circulatory compensation in 2 patients (T.J. and B.E.).

Table IV summarizes the effects of Su-5879 in 13 ambulatory hypertensive patients who were not in congestive heart failure. All of these had essential hypertension except 2 (H.M. and G.Y.); these 2 had primary renal disease. The simultaneously administered antihypertensive drugs, which are listed in

the table, had been given for at least 3 weeks prior to beginning the use of Su-5879, and were continued at the same dosage throughout the study. No patients had elevated levels of blood urea nitrogen.

TABLE IV. EFFECTS ON BLOOD PRESSURE OF SU-5879 IN HYPERTENSIVE PATIENTS NOT IN CONGESTIVE FAILURE

PATIENT	OTHER DRUGS	DAILY DOSAGE (MG.)	CONTROL B.P. (MM. Hg)	FINAL B.P. (MM. Hg)	CHANGE IN MEAN B.P.	WEEKS OF THERAPY
L. B.	Su-3118	100	190/110	150/92	−25	9
S. J.	Su-3118	150	176/104	156/100	− 9	4
H. P.	Rauwolfia Apresoline	100	200/110	168/98	−19	4
T. M.	Su-3118	100	175/116	140/90	−29	2
C. P.	Su-3118	100	186/124	150/98	−29	6
J. B.	Reserpine	100	226/126	140/98	−47	3
W. J.	Su-3118	100	186/110	154/94	−21	5
H. M.	Su-3118	100	210/120	210/116	− 3	2
G. Y.	Su-3118	100	220/130	210/120	−10	4
M. C.	Su-3118	100	216/126	145/100	−41	2
M. T.	Su-3118 Ansolysen	100	214/134	160/90	−47	3
M. F.	Su-3118	100	230/130	170/94	−51	7
T. B.	Su-3118	50	198/130	150/90	−43	5

In this group, Su-5879 at a dosage usually of 50 mg. twice daily resulted in a fall in mean blood pressure of 20 mm. Hg or more in 9 patients. The fall occurred within the first 1 to 2 weeks, and was maintained throughout the period of therapy. In 3 patients the diastolic pressure was decreased to 90 mm. Hg. Although all of the patients showed a decrease in blood pressure, the 2 with primary renal disease showed a relatively poor response. Levels of blood urea nitrogen remained within normal limits.

DISCUSSION

Su-5879 appears to be a clinically effective oral diuretic which is well tolerated. The initial oral doses of 300 mg. for hospitalized patients, and maintenance doses of 50 mg. three times daily, were apparently higher than necessary in most cases. The later regimen of 200 mg. for initial action and 50 mg. twice daily for maintenance was just as effective in our patients.

The diuretic effect appears to be similar to that of the mercurials and chlorothiazide, in that urinary volume is augmented, with predominantly an excretion of sodium and chloride to about 3 times the control levels. Excretion of potassium was increased to a maximum of 50 per cent above the control, but during the second week of observation it increased slightly above this level, while the excretion of sodium diminished. Levels of serum potassium below 4.0 mEq./liter were observed in only 2 patients during short-term hospital therapy. However, in the outclinic group, 6 of 19 patients developed levels of potassium below 4.0 mEq./liter after therapy of from 2 to 6 weeks. One outclinic patient developed

clinical symptoms of hypopotassemia, and this patient became asymptomatic upon the discontinuance of Su-5879 and the administration of oral potassium.

Although none of our patients developed serious renal insufficiency, the rise in the values of blood urea nitrogen observed in some indicate a need for caution in the administration of this drug. Two hospitalized patients with slight initial elevations of blood urea nitrogen and 3 others with initially normal values showed a moderate rise after short-term therapy. However, 3 other hospitalized patients with initial elevations of blood urea nitrogen showed a decrease after treatment. In the ambulatory patients with edema, 4 with slight elevations of blood urea nitrogen and 4 others with initially normal values showed slight rises after several weeks of therapy. No serious uremic complications occurred, and urinalyses in these showed no adverse changes.

Determinations of blood pressure before and after the administration of Su-5879 to patients with hypertension demonstrate a significant fall in 18 of 26 patients. The decrease in pressure was most dramatic in the patients not in congestive heart failure, but these as a group had a higher initial pressure than the patients in failure. Since most of the nonfailure patients were receiving Su-3118 (syrosingopine, Ciba) before and throughout the study, the more dramatic reductions in blood pressure in this group may have resulted from the potentiating effects of this reserpine derivative. None of the compensated hypertensive patients had significant adverse effects of blood urea nitrogen after therapy with Su-5879.

SUMMARY

1. Su-5879 (hydrochlorothiazide, Ciba) has been demonstrated to be an effective diuretic of low toxicity in studies on 19 hospitalized and 17 outclinic patients in congestive heart failure.

2. The diuretic effect is similar to that of the mercurials and chlorothiazide, in that there results mainly an outpouring of sodium and chloride, with a decrease in the levels of chloride and an increase of CO_2 in the serum.

3. A single dose of 200 mg. produces a conspicuous diuresis within about 2 hours after ingestion, and this is maintained for over 24 hours. Effective diuresis can also be achieved by doses of 50 mg. administered twice daily.

4. Excretion of potassium was increased moderately, and in a few patients levels of serum potassium below 4.0 mEq./liter appeared after 1 week of therapy. However, only one patient in our series had clinical symptoms of hypopotassemia.

5. Slight elevations in blood urea nitrogen after therapy were observed in some of our patients in congestive heart failure. None developed serious renal insufficiency. If oliguria develops and the blood urea nitrogen rises under treatment, the drug should be withdrawn.

6. Significant reductions in blood pressure occurred in 18 of 26 hypertensive patients. The antihypertensive action of Su-5879 appears most promising.

7. Su-5879 produced no serious complications in our cases. However, the resulting low values for serum potassium in a few of our patients, and the occasional moderate rises in values of blood urea nitrogen would, as with chlorothiazide, call for caution in long-term therapy.

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Flare-Up of Pericarditis Complicating Myocardial Infarction After Two Years of Steroid Therapy

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Pericarditis may occur as a complication of myocardial infarction and is then often associated with pleurisy and pneumonitis. The condition has been referred to as postmyocardial infarction syndrome.[1] It has a characteristic tendency to recurrences, resembling in this as in other respects the postcommissurotomy syndrome. Both conditions are dramatically relieved by corticosteriods. Withdrawal of hormones is usually followed by a mild rebound. In occasional instances, however, the flare-up is severe and may occur repeatedly after months or even years of steroid therapy. The case to be reported here is of interest because pericarditis with effusion developed 12 months and again 27 months after onset of myocardial infarction, when administration of steroids was discontinued.

CASE REPORT

S.M., a 58-year-old man, was admitted for the first time to the Maimonides Hospital on April 15, 1958, for withdrawal of steroids. The history given by the patient and his family physician, and study of records of admission to other hospitals, revealed the following data.

On Feb. 15, 1956, the patient suffered an attack of severe precordial pain and was hospitalized on that day. An electrocardiogram indicated an acute anterolateral wall infarction. The immediate course was stormy, marked by profound fall in blood pressure and dyspnea. On the second hospital day hemorrhagic expectoration developed, associated with severe pain in the left side of the chest, which was aggravated by breathing and turning in bed. Signs of consolidation at the left pulmonary base were noted. Pulmonary infarction was thought to be the cause. On the ninth hospital day the pulmonary signs subsided, and the temperature fell to 100° F. On the fifteenth day pain appeared at the right side of the chest and back, worse on deep breathing, and the temperature rose to 101° F. There was no more bloody expectoration, nor were signs of thrombophlebitis in the legs noted. The patient was transferred to another hospital on the nineteenth day of illness.

Low-grade fever was present again and was attributed this time to a urinary infection. However, fever persisted after the urinary infection had responded to the administration of Furadantin and Chloromycetin. On the twenty-third day of illness, while the patient still received antibiotics, the temperature rose to 102° F. Severe chest pain aggravated by breathing

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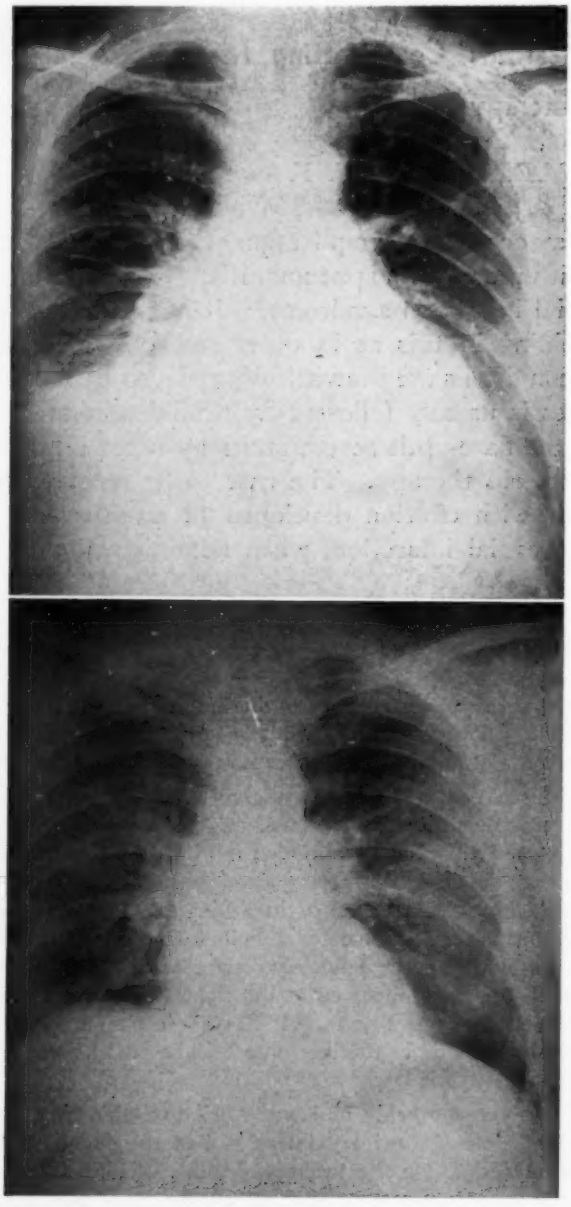
was again a prominent complaint. Pneumonia was diagnosed, and Achromycin was substituted for Chloromycetin. In the following 2 weeks the rectal temperature did not rise above 100° F., and the patient was discharged on March 24, 1956.

At home, during the first 10 days, low-grade fever was observed. On the fiftieth day of illness the temperature climbed to 103° F. Achromycin was then replaced by penicillin and streptomycin. On the fifty-sixth day the temperature rose to 103.6° F., and the patient complained



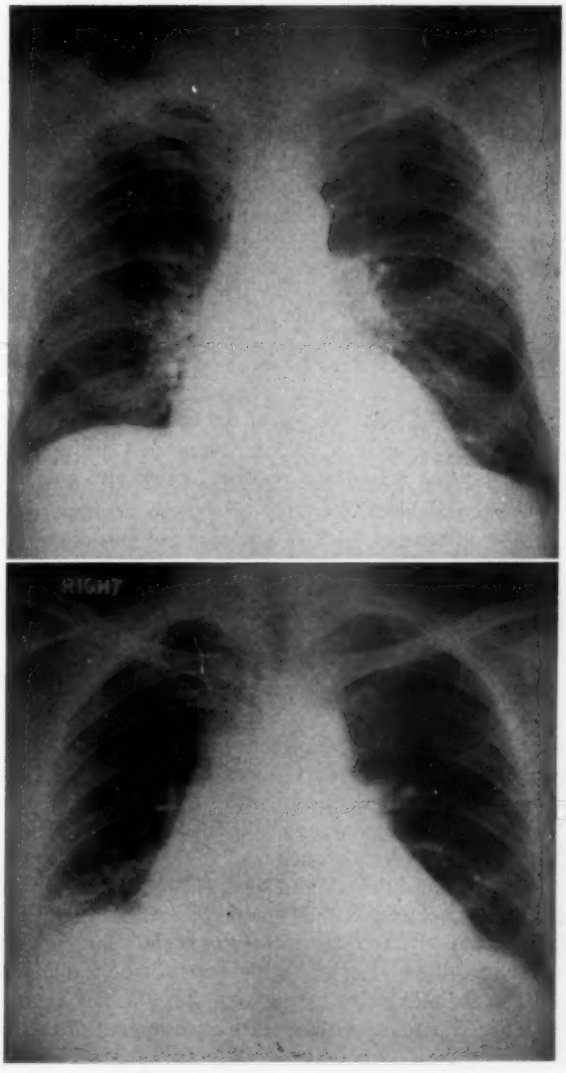
A.

B.

Fig. 1.—*A*, Feb. 26, 1957. The heart silhouette is enlarged, and its shape is triangular. A patch of infiltration appears at the right heart border. The left costophrenic sinus is obscured. The changes are consistent with pericardial effusion, pneumonitis, and pleural effusion. *B*, March 12, 1957. The size of the cardiac silhouette is diminished, and its shape is no longer triangular. Shading of the left costophrenic sinus and pulmonary infiltration have largely cleared.

again of marked chest pain. A bedside x-ray study showed a "large cardiac silhouette" and shading of both lower lung fields. At no time after the first few days of illness was there bloody expectoration. On April 11, 1956, a chest specialist was consulted; he diagnosed a postmyocardial infarction syndrome and advised administration of steroids. Meticorten was given at an initial daily dose of 30 mg. It caused rapid relief of fever and chest pain, so that the patient was soon able to leave his bed and lead a normal life as long as the daily maintenance dose of Meticorten was no less than 15 mg. Attempts at reduction of the dose below this level were made three times within 9 months, and invariably resulted in flare-up of fever and chest pain. Usually after 48 hours the family physician increased the daily maintenance dose, and the patient felt well again.

When I saw the patient for the first time 10 months after onset of his illness, he was free of complaints, receiving a daily maintenance dose of 15 mg. of Meticorten. Physical examination and x-ray studies revealed no abnormality other than moderate enlargement of the left ventricle



A.

B.

Fig. 2.—*A*, May 12, 1958, six days after withdrawal of steroids. The chest film shows moderate enlargement of the left ventricle, similar to the findings in Fig. 1,*B*. *B*, May 21, 1958, fifteen days after withdrawal of steroids. The cardiac silhouette has increased; its shape is triangular, and the waist is widened. The right costophrenic angle is obscured.

and, possibly, congestive heart failure. The blood pressure was 118/96 mm. Hg. The electrocardiogram showed residual signs of anterior wall myocardial infarction. It seemed advisable to attempt withdrawal of the steroids under close supervision in a hospital.

The patient was admitted to a hospital under the care of his family physician on Feb. 18, 1957. The maintenance dose of Meticorten was reduced every day by 2.5 mg. An x-ray study of the chest on Feb. 20, 1957, showed moderate enlargement of the left ventricle. On February 23, when the maintenance dose of Meticorten was reduced to 2.5 mg., the patient developed fever and pressing pain in the upper dorsal region, which was aggravated by deep breathing and twisting of the body. On February 26, x-ray examination indicated that the heart silhouette had increased and its shape had turned almost triangular (Fig. 1,*A*). A patch of infiltration was noted near the right heart border, and the left costophrenic sinus was obscured. The changes were interpreted as consistent with pericarditis, pneumonitis, and pleurisy.

I was called again to see the patient on Feb. 26, 1957, when his blood pressure had dropped to 65/50 mm. Hg and urinary secretion had all but ceased. The electrocardiogram, however, showed no additional changes. Administration of ACTH in addition to increased doses of Meticorten was advised. Fever and chest pain promptly subsided, the blood pressure rose, and renal function returned to normal. A repeat x-ray study of the chest, on March 12, 1957, showed diminution in the size of the cardiac silhouette and return to its former shape (Fig. 1,*B*). Shading of the left costophrenic sinus and the pulmonary infiltration had largely cleared. During convalescence the patient suffered a saddle embolism in the aorta and underwent successful embolectomy. Long-term anticlotting therapy was instituted. In addition to a daily maintenance dose of 15 mg. of Meticorten the patient received periodically injections of ACTH.

In the following year two unsuccessful attempts at withdrawal of steroids were made by the family physician. In March, 1958, I advised that the patient be admitted to the Maimonides Hospital for gradual withdrawal of steroids.

On admission the patient appeared to be in good condition. The heart rate was 62 per minute, and the blood pressure was 122/66 mm. Hg. There was no evidence of congestive heart failure. The lungs were clear. The apical thrust of the heart was felt in the fifth intercostal space and was of heaving quality. The area of cardiac percussion dullness was not enlarged. The heart sounds were fair. The heart action was regular. Liver and spleen were not palpable.

Laboratory Data.—Urine and blood electrolytes showed no abnormality. The white blood count was 12,300 per cubic millimeter, with 74 per cent polymorphonuclear cells; sedimentation rate (Wintrobe) was 12 mm. per hour; serum cholesterol was 262 mg. per cent; urea nitrogen was 18 mg. per cent; fasting blood sugar was 66 mg. per cent. The electrocardiogram revealed residual changes of anterior wall myocardial infarction. X-ray study of the chest, on April 18, 1958, indicated moderate enlargement of the left ventricle.

Course.—Anticoagulant therapy was continued, but it proved difficult to maintain a steady therapeutic prothrombin level. On occasions the prothrombin time rose to 47 seconds, but no signs of hemorrhage were observed. The maintenance dose of Meticorten, which had been 10 mg. during the preceding months, was gradually reduced to zero over a period of 17 days. During this time the patient received three injections of ACTH. After Meticorten was discontinued on May 3, 1958, ACTH was given for 3 days in diminishing doses, from 30 to 10 units per day. On May 6, all hormone therapy was discontinued. The patient's reaction was mild at first. He complained about vague pains in chest and back, which lasted but a few minutes and were not aggravated by breathing or change in body posture. In fact, the patient was able to be up and around all the time, although there were occasional rises in temperature, the highest being 101.2° F. on May 9, that is, 3 days after the withdrawal of hormones. The white blood count dropped to normal, but the sedimentation rate rose to 22 mm. per hour. An x-ray study of the chest, on May 12, 1958, (Fig. 2,*A*) showed moderate enlargement of the left ventricle such as had been noted on previous occasions. For a few days crackling râles were heard over the right pulmonary base. When these disappeared and the temperature was below 100° F., the patient was discharged on May 16, that is, 11 days after discontinuance of the hormone therapy.

At home the patient was comfortable for 3 days. Then, the temperature rose to 101° F., and pressing pain was felt in the region of the lower sternum, associated with deep breathing.

Since fever and chest pain became worse on the following days, the patient was admitted for the second time to the Maimonides Hospital on May 21, 1958.

On admission the temperature was 103.2° F., the heart rate was 106, and the blood pressure was 105/78 mm. Hg. The cervical veins were not distended, nor were there other signs of congestive heart failure. Moist râles were heard over the right base of the lungs. The apical thrust of the heart was not felt. There was marked percussion dullness over the upper half of the sternum and in adjacent areas, extending to the left from one to two inches in the second and third intercostal spaces. The heart sounds were distant. No pericardial friction rub was heard.

Laboratory Data.—The white blood count was 14,700, with 80 per cent polymorphonuclear cells. The sedimentation rate (Wintrobe) was 29 mm. per hour. The urine showed initially 1+ albumin and "many red blood cells." These changes cleared in the following few days. The electrocardiogram was not different from that observed on previous admission. X-ray study of the chest, on May 21, indicated that the heart silhouette had become larger in the past 9 days, its shape triangular, and the waist markedly widened (Fig. 2,*B*). The right costophrenic angle was obscured. The venous pressure measured 13 cm. of water, and rose to 23 cm. upon pressure in the right upper abdominal quadrant.

Course.—A pericardial paracentesis, on May 22, yielded 300 c.c. of a straw-colored fluid, which contained numerous polymorphonuclear cells. Its specific gravity was 1.020, and its protein content was 4.9 Gm. Culture and smear of the pericardial exudate revealed no microorganisms. Two blood cultures were negative. A search for lupus erythematosus cells was unsuccessful.

The temperature fell to 100° F. on the fifth hospital day, and rose again gradually to 101.4° F. Chest pain was greatly relieved. On the eleventh hospital day the white blood count was 8,200, with 72 per cent polymorphonuclear cells. The sedimentation rate, however, was 32 mm. per hour.

After pericarditis was diagnosed, anticlotting therapy was discontinued. The patient's condition seemed to improve. An x-ray film, on May 27, indicated almost complete clearing of the pleural effusion and slight diminution in the size of the heart silhouette. Hope was entertained that improvement would this time progress to healing without resumption of hormone therapy. However, the family physician urged that the patient be given steroids again. When this was refused, the patient requested to be discharged from the hospital.

DISCUSSION

The case reported here showed a remarkable sequence of events following acute myocardial infarction. The initial febrile period was prolonged and characterized by pleuropericardial pain and hemorrhagic expectoration. Pulmonary infarction was thought to be the cause. However, fever and chest pain of pleuropericardial type continued relapsing for 8 weeks, while hemorrhagic sputum was no longer present. Nor did the electrocardiogram reveal evidence of an extending myocardial lesion. The diagnosis was then changed to recurrent pneumonia. Numerous antibiotics failed to influence the febrile course. In the eighth week of illness, when the chest film indicated enlargement of the heart silhouette in addition to pleurisy, a postmyocardial infarction syndrome was diagnosed; steroid therapy was instituted and abruptly relieved all manifestations of the illness. However, repeated attempts at withdrawal of the hormones resulted in flare-ups of fever and chest pain. On two occasions, that is, 10 months and 2 years, respectively, after onset of steroid therapy, discontinuance of hormone administration produced symptoms and signs of pericardial effusion, pleuritis, and pneumonitis.

We have observed similar severe and recurrent withdrawal reactions in two other cases of postmyocardial infarction syndrome, in one of which signs of

adrenal insufficiency developed, necessitating continuation of hormone therapy for a prolonged period of time. These drawbacks have to be borne in mind when the question of the use of hormones arises. Some patients suffering from postmyocardial infarction syndrome do not require steroids because the complication may subside spontaneously after a short time. Hormone therapy should be reserved for severe cases with prolonged course and intractable pain.

Flare-ups of the basic disease, occurring after many months or years of steroid therapy, have been observed in various conditions, as for instance, in the postcommissurotomy syndrome, also in collagen diseases such as rheumatoid arthritis, periarteritis nodosa, and lupus erythematosus. The observations made in the case of this report are of some significance with regard to the etiology of the postmyocardial infarction syndrome. It is unlikely that we are dealing with an infectious process, for it is known that steroids, while suppressing the inflammatory manifestations, facilitate the growth of microorganisms. No evidence of spread of infection was observed in the present case. In fact, in the cases of postmyocardial infarction syndrome so far investigated, the search for microoragnisms in cultures and pericardial and pleural effusions was unsuccessful. We suspect that sensitization by necrotic heart muscle is the cause of the inflammatory condition which occasionally complicates acute myocardial infarction.

SUMMARY

A case of myocardial infarction is reported in which the acute stage was complicated by recurrent febrile episodes and pleuropericardial pain. Postmyocardial infarction syndrome was diagnosed. Administration of corticosteroids brought prompt relief. Repeated attempts at withdrawal of the hormones resulted in relapse of fever and chest pain. Steroid therapy was continued for more than 2 years. On two occasions, that is, 10 months and 2 years, after institution of steroid therapy, withdrawal of hormones was followed by development of pericarditis with effusion, pleuritis, and pneumonitis.

The observations made in this case offer another argument against the view that the postmyocardial infarction syndrome is of infectious origin.

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Atrial Parasystole

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Parasystole is an arrhythmia caused by the firing of automatic impulses in an ectopic center not related to and undisturbed by the existing sinus rhythm. The presence of such a center in the ventricles is not a rarity, since it has been estimated to be present once in every 1,200 electrocardiograms taken in a general hospital.[12] However, only a few instances of atrial parasystole have been described. In this paper two such cases will be reported.

OBSERVATIONS

Observation 1.—W. J., a 49-year-old man, was admitted to the hospital because of ankle edema and dyspnea on exertion which had developed in the few days prior to admission. He had been hospitalized two months before in another hospital because of "black outs." On examination the heart was found to be moderately enlarged to the left and a Grade 2 systolic murmur was audible over the apex. The blood pressure was 180/106 mm. Hg. The electrocardiogram showed the pattern of left ventricular hypertrophy. The diagnosis was hypertension and congestive heart failure.

The day after admission the patient developed a paroxysmal atrial tachycardia which stopped after the intravenous administration of 1.5 mg. of digoxin. However, an atrial arrhythmia persisted despite the daily administration of 0.5 mg. of digoxin.

The electrocardiograms obtained during the period of hospitalization showed sinus rhythm occasionally interrupted by an A-V rhythm with deeply inverted P waves in Leads II and III and a short P-R interval. The presence of premature atrial contractions was also noted during this period, and after analysis these were recognized as being due to an atrial parasystole.

Fig. 1 shows a strip of Lead II. Strips *A* and *B* of Fig. 1 are continuous. There is a sinus rhythm with a rate of 70. Changes in the form of the P waves are apparent. At the beginning of *A* and at the end of *B* some of the P waves are inverted and the P-R interval is shorter. These beats presumably originate in the upper part of the A-V node. In addition, there are P waves which are tall and peaked; in *A* these can be seen in the third, ninth, and fifteenth atrial complexes, and in *B* they appear in the sixth and twelfth. These P waves appear at different times of diastole. They are separated from the preceding QRS complex by intervals of 0.50, 0.48, 0.41, 0.38, and 0.20 second. On the other hand, the intervals between these ectopic beats are fairly constant, measuring 441, 443, 448, and 430 hundredths of a second. The presence of ectopic atrial beats appearing at regular intervals in varying phases of diastole is indicative of an atrial parasystole.

Tracings taken on other days showed the same disturbance (Fig. 2). The rate of the sinus rhythm varied between 79 and 86. The same type of ectopic beats are present as in Fig. 1 (strips

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A, *B*, and *C* of Fig. 2 are continuous). The intervals between the ectopic P waves and the preceding QRS complex are 0.48, 0.40, 0.41, 0.37, 0.36, 0.38, 0.35, and 0.44 second. The interectopic intervals are 443, 446, 444, 446, 448, 444, and 452 hundredths of a second.

At several places in the tracings in Fig. 2, two ectopic abnormal P waves follow each other directly without a sinus beat being interspersed. This phenomenon is not seen after the first ectopic beat of *A*, but it appears after all the others. The distances between two such ectopic beats measure 0.84, 0.83, 0.84, and 0.83 second. This may represent the ectopic interval which thus is directly measurable. If this is the case, the long interval of 444 hundredths of a second is equal to five times 0.88 second. Therefore, it is possible that a center forms impulses every 0.88 second and that every fifth impulse elicits a response, with the exception of those areas where two impulses are answered in succession. The interval between two successive abnormal P waves, which was found to be 0.83 to 0.84 second, fits well into this explanation. An atrial parasystolic rhythm may vary from beat to beat by a few hundredths of a second.

Observation 2.—L. C., a 56-year-old man, was admitted to the hospital because of dyspnea and ankle edema. There was a long history of hypertension. On admission the typical mid-diastolic murmur of mitral stenosis was heard over the apex; the blood pressure was 180/100 mm. Hg. For the past several months he had been taking 0.1 mg. of digitoxin daily. He was dismissed from the hospital within 24 hours, but was readmitted in shock 3 months later, and expired shortly after admission. The diagnosis was mitral stenosis, hypertensive heart disease, coronary sclerosis, and acute myocardial infarction. The electrocardiograms were taken during the first admission. There was a sinus rhythm interrupted by ectopic atrial beats. The P-R interval was 0.26 second. The ventricular complexes showed the pattern of left ventricular hypertrophy.

Tracings *A* and *B* in Fig. 3 represent Lead I taken at different times, while *C* is Lead II. In tracing *A* the intervals between the ectopic beats and the preceding QRS complexes measure 0.26, 0.26, 0.24, 0.18, 0.34, and 0.26 second; in *B* these values are 0.41, 0.37, 0.42, 0.28, and 0.26 second; and in *C* the intervals are 0.16, 0.24, 0.42, 0.28, 0.32, and 0.24 second. The interectopic intervals expressed in hundredths of a second are: in *A*: 236, 322, 226, 240, and 220; in *B*: 206, 206, 210, 205, and 220; and in *C*: 228, 89, 232, 220, 308, and 224. The sinus period averages 0.84, 0.72, and 0.80 second in *A*, *B*, and *C*, respectively.

Here again the appearance of ectopic beats at regular intervals and at varying phases of diastole points to the presence of a parasystole. It will be noted that on two occasions the measured interectopic interval is longer. Thus, in Fig. 3,*A* the intervals vary between 220 and 240. It is quite possible that there is a 3:1 block; thus, the actual interval would be between 75 and 80. In the one long interval in this tracing the time is 322, which is about 82 hundredths of a second longer; in other words, the block has changed from 3:1 to 4:1. In the second tracing the measured interectopic intervals are 206 to 220, and a 3:1 block with an actual interval of 68 to 73 is possible. In Fig. 3,*B* the sinus rate was appreciably faster than in Fig. 3,*A*. In the third tracing the intervals vary between 220 and 232 hundredths of a second, except for one which is 308 or 76 to 88 hundredths of a second longer. The observation that some measured interectopic intervals are longer than the usual ones by almost exactly the calculated single interectopic period is strong evidence for the presence of parasystole.

As in the first case the first beat following an ectopic beat exhibits occasionally the same form of P wave as the ectopic one. This can be seen in Fig. 3,*C*. The interval between these beats is 0.89 second and may represent a directly measurable interectopic interval.

The presence of an atrial parasystole is even more evident in Fig. 4, obtained on the same day from the same patient. The tracing again reveals the atrial ectopic beats in different phases of diastole. The two strips are continuous and the successive interectopic intervals are 314, 220, 216, 224, 90, 220, 90, 220, and 216 hundredths of a second. On two occasions two ectopic beats occur in succession, and if both impulses are due to activity of the parasystolic center, we are again able to measure the interectopic interval directly. It appears that the center is emitting impulses at a rate varying between 90 and 110 hundredths of a second, and in most instances there is a 2:1 block; the block changed to 3:1 in one instance when the interval became 314 or 94 hundredths of a second longer than the others. The seventh atrial complex in Fig. 4,*A* shows a different P wave. This is a combination beat caused by the simultaneous formation of the normal and ectopic impulses so that each activates parts of the atria at the same time.

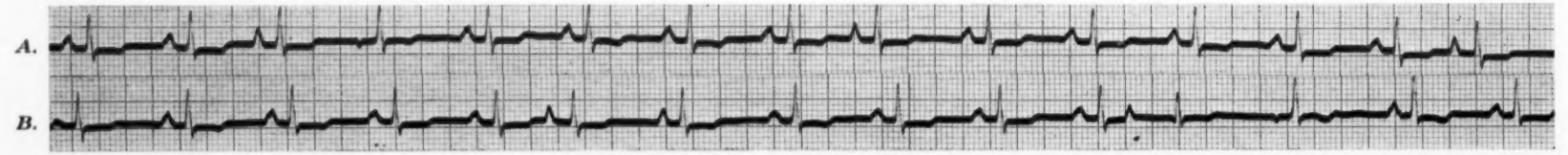

Fig. 1.—Observation 1: *A* and *B* are continuous. Periodically, at regular intervals, large, peaked P waves appear, caused by atrial parasystole. One beat with inverted P waves in *A* and one in *B* is caused by an A-V beat.

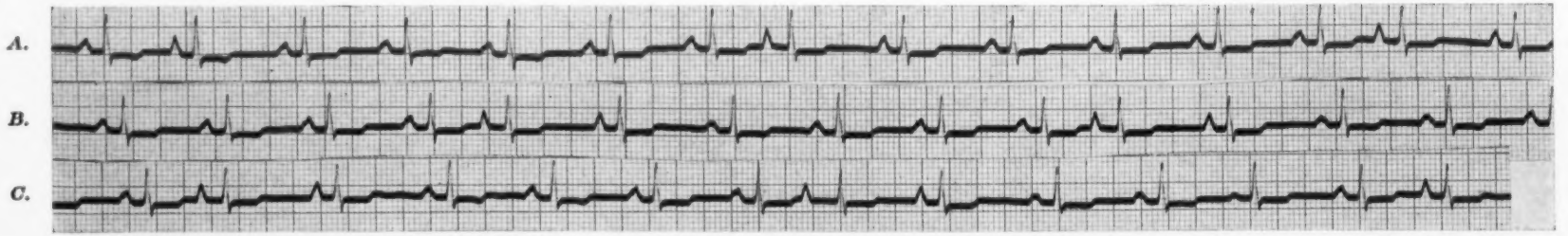

Fig. 2.—Observation 1: The three strips are continuous. At several places two ectopic beats follow each other directly, permitting direct measurement of the ectopic interval.

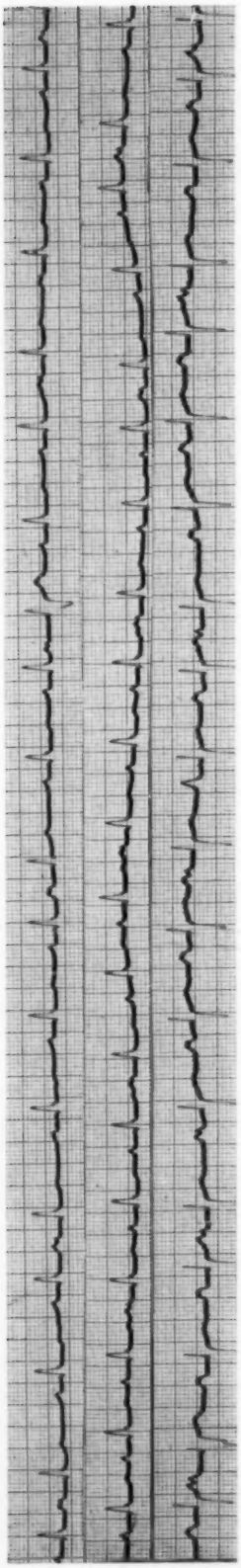

Fig. 3.—Observation 2: Three tracings obtained at different times demonstrating atrial parasystole.

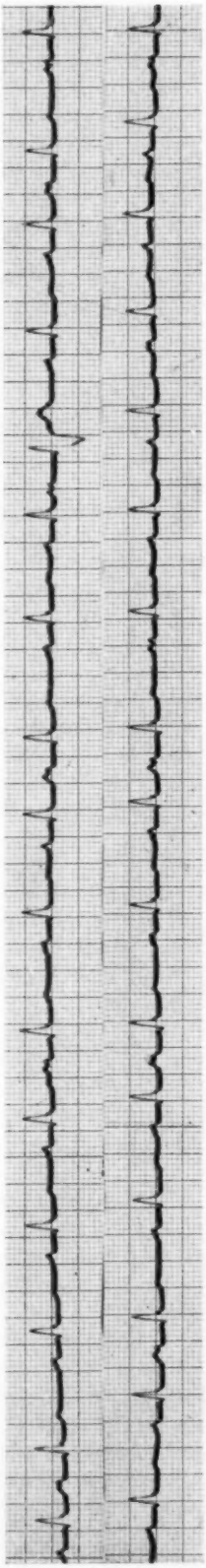

Fig. 4.—Observation 2: The two strips are continuous. Atrial parasystole with direct succession of two ectopic beats on two occasions.

DISCUSSION

There is an important difference between the mechanisms of atrial and ventricular parasystole. In the latter there is a simple interference between the two rhythms, the basic rhythm, which usually is sinus rhythm but occasionally may be atrial flutter or fibrillation, and the ectopic, parasystolic rhythm. Each center works independently of the other, and each impulse from either center upon reaching the ventricles outside of their refractory period elicits a response. Occasionally, the ectopic impulse may be reversely conducted to the atria and on reaching the sinus node disturb the rhythm. In atrial parasystole the ectopic center is similarly uninfluenced by the sinus rhythm; it is "protected." This protection is the essential factor for the appearance of any parasystole. However, the ectopic impulses reach the sinus node and disturb the impulse formation so that there is a union between the two rhythms. Therefore, in atrial parasystole the same cycles, the same patterns, may appear in the electrocardiogram again and again; there is less variation of coupling, and the presence of combination beats due to the almost simultaneous appearance of a sinus and ectopic impulse, each activating parts of the atria, is rare.

The first patient with atrial parasystole was observed by Kaufmann and Rothberger.[4] No tracing or clinical data were given. Another case, that of a healthy 25-year-old man, was described by Jervell.[3] The coupling varied between 0.26 and 0.6 second, the sinus rate was 90, and the ectopic rate 50. All interectopic intervals could be divided by a common denominator, the smallest interval. A third patient, an 84-year-old woman, was described at Attinger.[1] The patient had coronary sclerosis and hypertension. The ectopic rate was about half the sinus rate. In a 32-year-old, apparently healthy man described by Vedoya[14] the sinus intervals were 0.74 to 0.92 second and the ectopic intervals were 0.49 to 0.85 second. Another case, described by Scherf and Schott,[12] was that of a 59-year-old man suffering from an acute anteroseptal infarction. The sinus rhythm was about 78, and the ectopic rhythm was 22. It is probable that the rate of impulse formation in the ectopic center was actually 44 per minute and that every second impulse was blocked.

In all probability, the rate of the parasystolic rhythm represents the natural rate of a pacemaking fiber. When the center is in the ventricle, the rate of the pacemaker may be assumed to be relatively slow, whereas in atrial parasystole the rate can be expected to differ only slightly from the existing sinus rhythm.

The possibility, in both observations, of measuring directly the interval of the parasystolic rhythm because of the presence of two consecutive ectopic beats is of particular interest because this has not been possible in other cases. The appearance of an automatic atrial beat following a premature one with identical P waves is a phenomenon which was first described by Lewis. The P wave of the beat following an atrial extrasystole may have the same form as the extrasystole. Lewis assumed that the extrasystolic impulse in some manner precipitates a discharge of the next automatic impulse appearing just before the next sinus impulse is due. The phenomenon was "considered to be the result of slight quickening of physiological impulse formation in the area in which the premature beat arises."[5] Later, the same phenomenon was seen clinically

and experimentally in the ventricle[6] and could be easily provoked in a dog by electrical stimulation of the atria.[13] Both clinically and experimentally it is interesting to note that the first postextrasystolic beat is abnormal but does not necessarily have the same form as the extrasystole. It is possible, therefore, that at least in some instances we may be dealing with the phenomenon of "after discharge"; two or more stimuli applied in rapid succession may cause in certain cells the firing of one or more extra impulses. The rate of this after-discharge in the dog heart under various conditions is approximately the same as that of the prevailing basic rhythm.[9] In our cases an after-discharge is improbable since we are dealing with a parasystole and not with extrasystoles.

In both of our observations the heart was abnormal. It has been stressed previously that ventricular parasystole is seen only in diseased hearts.[2] This point of view is not shared by Vedoya,[14] who considers the presence of parasystole no more significant than that of extrasystoles. However, in the five cases of parasystole described by this author only the one with an atrial parasystole appears to have had a healthy heart; the others had evidence of heart disease—one suffered from angina pectoris, two others had hypertension, and the fourth had a paroxysmal ventricular tachycardia, which is usually associated with organic heart disease. We recently had the opportunity of observing a parasystole in a 26-year-old colleague who smoked 17 cigarettes a day. The arrhythmia cleared promptly when smoking was discontinued. There were no abnormal findings in the cardiovascular system of this patient, but it is possible that a relationship existed between the arrhythmia and the smoking.

Both of our patients exhibited the parasystole while on digitalis therapy. This has been observed before in ventricular parasystole, and transition from parasystolic to extrasystolic impulse formation under the influence of this drug has been seen.[12] However, the relationship between digitalis therapy and this arrhythmia has not been studied.

The regular spacing of the ectopic beats shows that the automatic atrial center is not disturbed by the sinus rhythm; it is protected. The nature of the protection is unknown but the existence of a block around the center has not been actually proved and is improbable.[2,10] In experiments on dogs it could be demonstrated that a rapidly working center, sending out frequent impulses, will not be influenced by other impulses spreading over the heart, since the rapid impulses emitted from the center do not let any other impulses penetrate it.[8] When the parasystolic rate is slow, it is always possible that the active center is more rapid and that a 2:1 or 3:1 block exists. Actually, an instance of parasystole has been described in which a very rapid center emitted impulses at 166 beats per minute. Suddenly a 2:1 block set in and a typical interference of two rhythms with parasystole developed.[7] Experimental parasystole due to veratrine applied locally is also rapid and the same mechanism is probable responsible for the protection of the ectopic center.[11] It is doubtful, however, whether this mechanism operates in the majority of the other instances of this arrhythmia. If a center within the ventricle is protected, parasystole develops. The intrinsic automaticity of the deeper ventricular centers is a slow one, and the rates actually found are the expected ones. Therefore, another mechanism

must exist; its nature is unknown. We know that rhythmical impulse formation of automatic type is characterized by slow depolarization in diastole, which has been observed in all pacemaker cells. Such a depolarization should make these cells more, not less, excitable, and therefore it is not clear why they do not respond to the conducted impulse as normal cells do, and why they do not become completely depolarized, when an impulse spreads over the heart.

SUMMARY

Two patients with an atrial parasystole are described. In both instances ectopic atrial beats appear at different phases of diastole, independent of the existing sinus rhythm. The literature on this arrhythmia is reviewed and the rarity stressed. The mechanism of atrial parasystole is discussed.

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Combined Catheterization of the Heart Utilizing a Modified Transbronchial Technique, Percutaneous Left Ventricular Puncture, and Venous and Arterial Catheterization

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Simultaneous recording of left atrial, left ventricular, and aortic pressures in the diagnosis and evaluation of left-sided valvulopathies is of primary importance. Various techniques are being used at the present time with generally satisfactory results.[1-15] For the past two and one-half years we have used transbronchial puncture of the left atrium in the manner described by Allison and Linden[1,2] and Facquet and associates,[3] with the modifications introduced by Morrow.[4,5] Catheterization of the left ventricle has been accomplished by passing a small polyethylene tube through the atrial needle, across the mitral valve, and thence into the left ventricular cavity. We did not always find this method to be satisfactory. Most of our failures were due to lack of success in advancing the catheter into the left ventricle through the mitral valve, particularly in cases of significant mitral regurgitation. Although left atrial tracings were usually acceptable, in several instances the recordings were unsatisfactory or incomplete due to apprehension, ill feeling, cough, and respiratory irregularities obviously induced by the presence of the bronchoscope in the patient's tracheobronchial tree. It appears that this alters the intrathoracic and intracardiac pressures and certainly rushes the procedure.

It is our impression that the experience of others with percutaneous left atrial puncture through the back[6-11] is not significantly better insofar as left ventricular catheterization is concerned. In addition to this feature, the performance simultaneously of left ventricular puncture and percutaneous left atrial puncture is complicated not only by the additional risks of the latter, but also by the necessity for major changes in the patient's position and, under certain circumstances, difficulties in establishing comparable base lines.

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To simplify the transbronchial procedure a new, slotted bronchoscope* and a specially designed needle* have been used and have proved to be of great advantage to both operators and patients. By combining the transbronchial puncture of the left atrium, percutaneous puncture of the left ventricle,[12] and transarterial catheterization of the aorta, we have been able to obtain highly satisfactory data in patients with mitral, aortic, or combined valvulopathies.

INSTRUMENTATION AND TECHNIQUE

The bronchoscope is a 7 by 40-mm. instrument which has been built in such a way that part of its wall slides out in its entire length, leaving a longitudinal slot in the anterior part of the wall of the bronchoscope. The equipment used in bronchoscopy, and the atrial and ventricular needles are illustrated in Fig. 1. The proximal end of the atrial needle is connected to a length of polyvinyl tube 60 cm. long. This tube is connected by a 3-way stopcock to a P23Db Statham gauge. A bronchial foreign-body extracting forceps* is used as carrier to pass the needle into the bronchus. The ventricular needle* is an 18G thin wall, 6 inches long, with a pyramidally pointed stylet. It is connected to another P23Db Statham gauge by a 3-way stopcock and Saran tubing. For the recording of arterial pressure a No. 6 Cournand catheter is placed in the ascending aorta by advancing it through a brachial artery, or a polyethylene tube is placed using a Seldinger needle† in the femoral artery. This catheter is connected to a third P23Db gauge with a 3-way stopcock. The recording equipment consists of a 4-channel Sanborn recorder.

The patient is not allowed to eat or drink for 6 hours prior to the procedure and is given 2 grains of Sodium Luminal, and 1/150 grain of scopolamine 1 hour before the procedure. Demerol, 75 to 100 mg., or morphine, 1/6 grain, is given 15 to 20 minutes before bronchoscopy. The catheterization of the right side of the heart, if planned, is carried out in the usual way after placement of the arterial pressure catheter. The hypopharynx is sprayed with a small amount of 0.5 per cent solution of Pontocaine. Two to three cubic centimeters of 0.5 per cent Pontocaine is injected percutaneously into the trachea. After a few moments the bronchoscope is advanced to about 1 cm. below the carina in the left main-stem bronchus. After expelling all the air out of the needle and its tubing by flushing with heparinized saline, the needle is grasped behind the button with the forceps and advanced into the trachea. It is directed anteriorly and toward the midline, and is forced through the anterior wall of the left main-stem bronchus at the previously mentioned point 1 cm. below the carina, into the cavity of the left atrium. Once in place, the needle is released from the forceps and the latter is removed. The sliding part of the bronchoscope is then withdrawn so that the tubing coming from the needle can be taken out of the lumen of the bronchoscope, allowing removal of this instrument without disturbing either the needle or the tubing. The patient, who is in the supine position with head extended for bronchoscopy, is then made more comfortable. Percutaneous left ventricular puncture is performed after infiltration of the part of the chest wall overlying the point where the apex is palpated. Infiltration with 1 per cent procaine is accomplished in the full chest wall thickness to include the pleural layer. During introduction of the needle careful monitoring of the ECG by both the operator and the protocol recorder is essential. If irregularities occur, care is taken to allow time for adjustment of rhythm before proceeding further.

When the procedure has been satisfactorily completed, the ventricular needle is removed, keeping pressure over the area of puncture for 2 or 3 minutes. The atrial needle is easily withdrawn by simply pulling on the tubing. Needless to say, this should be fixed securely to the needle hilt. The patient is encouraged to cough frequently so that any bleeding may be detected. The bronchoscopic equipment is kept in readiness so that if bleeding should occur, it may be controlled by repeat bronchoscopy. To date, bronchial bleeding has not been a serious complication. The aortic catheter is left in place for an additional 15 to 20 minutes, during which time the systemic

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*Manufactured by Pilling & Company, Philadelphia, Pa. (Elliot, slotted bronchoscope. Forceps, Cat. No. Br 996).

†Manufactured by Stille, Sweden; Distributed in the U.S.A. by Ohio Chemical Company.

pressure is monitored. It is removed after assuring that the blood pressure remains stable. An x-ray of the chest is taken a few hours after the ventricular puncture so as to rule out pneumothorax.

Another method for registering left ventricular pressure is also used as an alternate to direct puncture and in preference to it in certain cases. This consists of retrograde catheterization of the left ventricle by advancing the No. 6 Cournand catheter through the brachial artery into the ascending aorta and through the valve. This technique was developed by Soulié, Carlotti, Joly, Sicot, and Voci in Paris in 1950.[13] Voci, working with Soulié, did the first retrograde catheterization of the left ventricle in a case of aortic stenosis in 1951.[14]

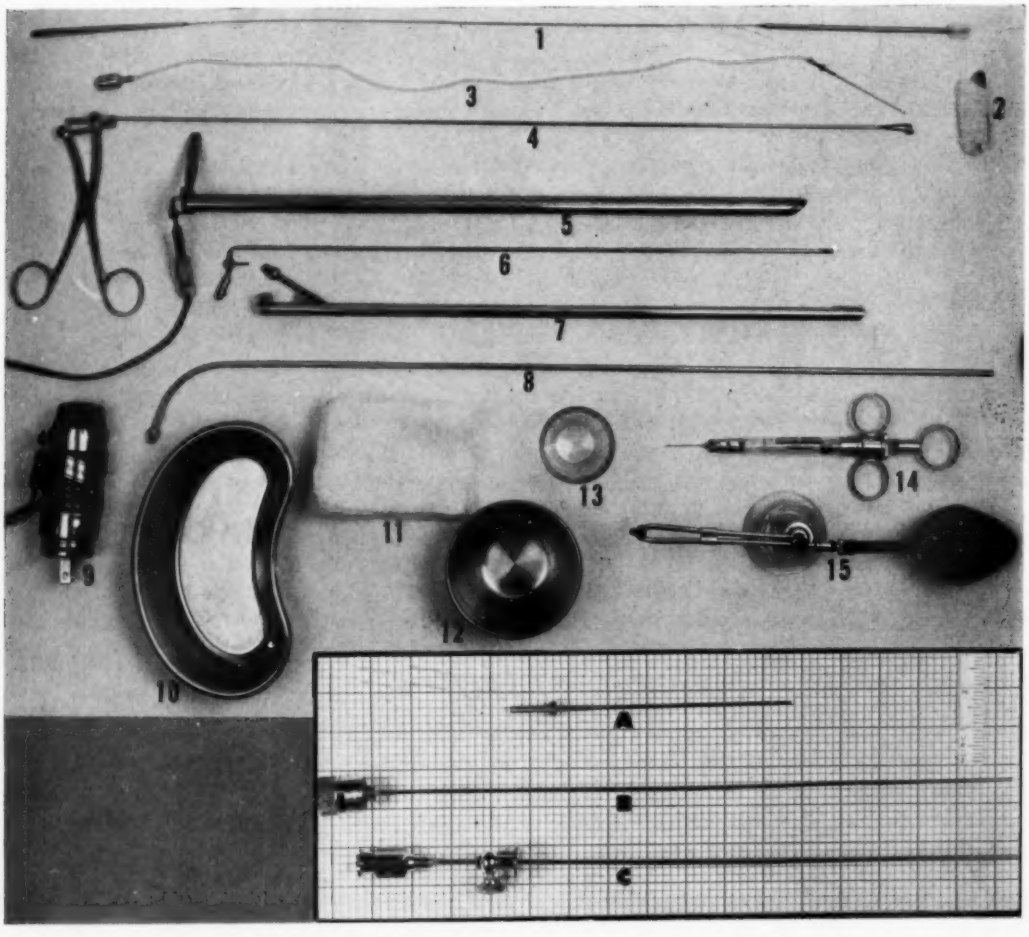

Fig. 1.—Photograph of the equipment which is essential in the performance of transbronchial left atrial puncture by the technique discussed in the text. *1*, Bronchoscopic sponge holder. *2*, Packet of sponges. *3*, Atrial needle with the polyvinyl tubing attached to it. *4*, A foreign-body grasping forceps with side grasping jaws. *5*, *6*, and *7*, Parts of the new slotted bronchoscope; *7* is the removable sheath. The slot is visible as a dark line along the length of the bronchoscope (*5*) on its lower side. *8*, Aspirator tip. *9*, Transformer for the bronchoscopic light (*6*). *10*, Small emesis basin. *11*, Gauze sponges. *12*, Small steel basin for saline. *13*, Medicine glass for Pontocaine solution. *14*, A 2-c.c. hypodermic syringe with a 25-gauge, one-inch needle. *15*, Atomizer containing 0.5 per cent Pontocaine. Inset: *A*, The left atrial needle, which is a 19-gauge, shallow bevel, side-ported needle adapted for connection to polyvinyl tubing with a button (visible on the left-hand end) which prevents excessive penetration. The hilt of the needle is so turned that it can be grasped firmly by the bronchoscopic forceps. *B*, The stylet of the ventricular puncture needle. This stylet has a trocar point which protrudes about 1 mm. from the end of the square-ended ventricular needle (*C*). *C*, The ventricular needle itself, a thin-walled, 18-gauge shaft which is 6 inches long. A small metal sleeve with a set screw is placed on the needle in order to mark its depth at optimum positioning. The large blocks in the background of the illustration are 1-cm. squares.

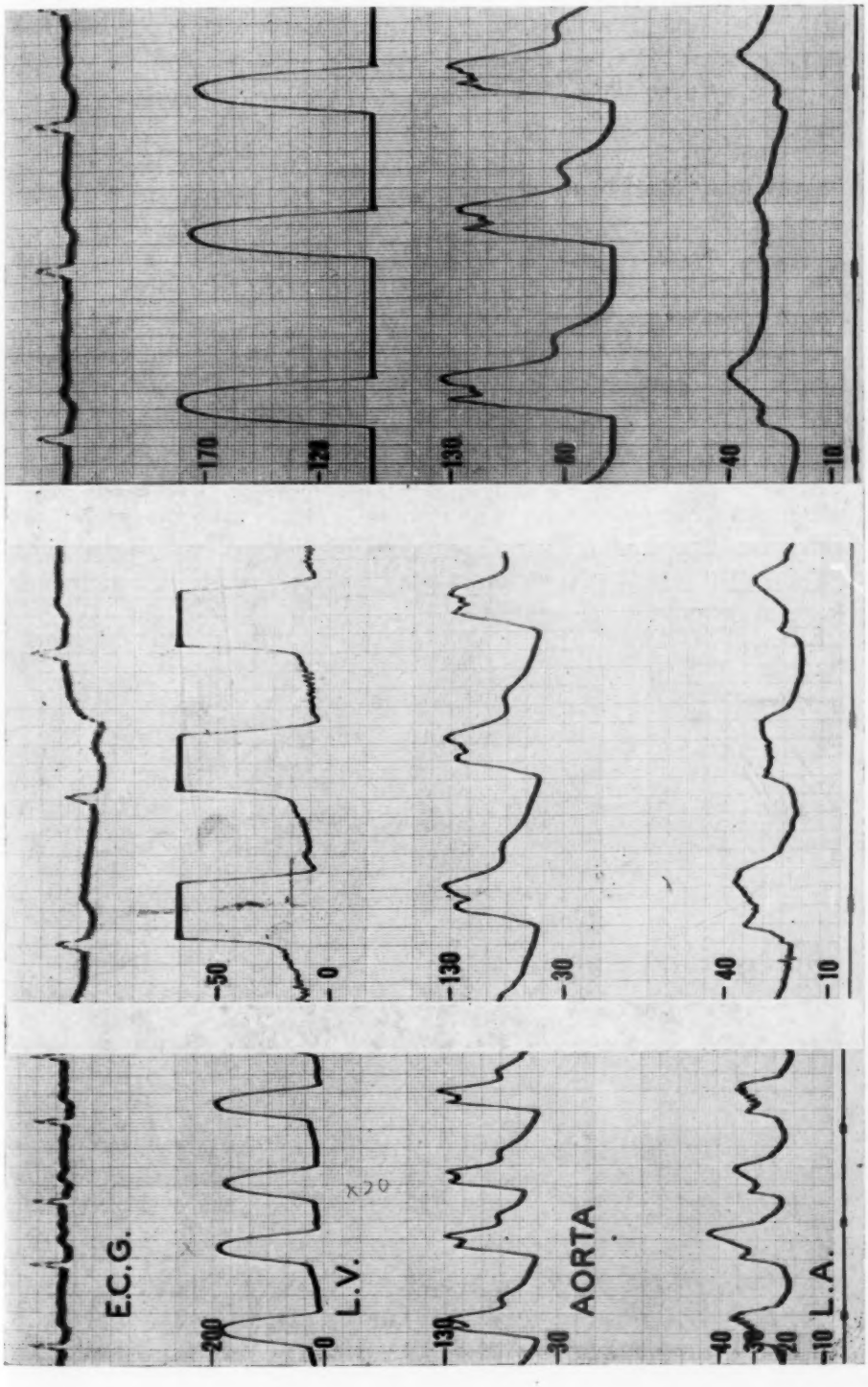

Fig. 2.—Tracings obtained in a case of aortic stenosis. On the left, from top to bottom, are the electrocardiogram, left ventricular, aortic, and left atrial pressure pulses without suppression. In the center are shown the ventricular diastolic pressure pulse and, at the bottom, the atrial pressure pulse to evaluate the transmitral diastolic gradient. On the right are shown the left ventricular peaks and the aortic peaks to evaluate the transaortic valvular systolic gradient.

RESULTS

During the past three years 116 cases have been studied by one or more of the techniques alluded to in this paper. In the beginning we were very much impressed by the transbronchial method of left atrial puncture as performed by Morrow. Its simplicity and safety made it our choice in preference to the then rather hazardous percutaneous left atrial puncture. As employed by us, transbronchial left atrial puncture by this technique proved to be moderately satisfactory. A total of 40 cases were studied. Three of these, however, were bronchoscopic failures, and, thus, the procedure was not carried out at all. Nine cases were studied twice; therefore, a total of 46 left atrial punctures was performed. In six of these instances unsatisfactory left atrial tracings were obtained. In only one instance was a satisfactory left ventricular tracing obtained, although in two or three other instances the catheter was passed into the ventricle, but could not be made to remain there long enough for tracings to be recorded. There were two instances of severe and alarming bronchial bleeding following the puncture. In both of these cases the patient recovered uneventfully. There was one death, in a severely ill patient who immediately upon withdrawal of the needle and bronchoscope had a convulsive type of reaction associated with cardiac arrest and with massive bronchial bleeding. These results led us to seek ways and means of improving this approach.

TABLE I

NUMBER OF CASES	NUMBER AND COMBINATIONS OF LEFT HEART PROCEDURES			
	LEFT ATRIUM (NEW TECHNIQUE)	LEFT VENTRICLE (PUNCTURE)	LEFT VENTRICLE (RETROGRADE)	FEMORAL ARTERY OR AORTA (CATHETER OR PUNCTURE)
22*	24	24	—	24
9	—	9	—	9
1	1	—	—	1
3	3	—	3	3
41*	—	—	43	43
76	28	33	46	80
Failures	3	3	12†	—

*Two cases in each of these groups were studied twice (preoperatively and postoperatively) by the same combination of procedures.

†Estimated figure.

Table I indicates the number of cases and the various combinations of procedures used since the modified technique of left atrial puncture was adopted. It will be seen that there has been a total of 28 left atrial punctures performed by this new method. In only one instance were the left atrial tracings of inferior quality. There were three other cases in which bronchoscopy was impossible. There have been no deaths in this series and only two complications. The compli-

cation in one case consisted of a period of prolonged hypotension followed by renal shutdown and subsequent recovery. This patient died of her disease about a month after the study. The second complication was in another patient in intractable congestive failure with mitral stenosis, in whom the studies led to an exacerbation of her state of congestion. In both of these cases right heart catheterization as well as left ventricular puncture and aortic catheterization had been performed. The use of a small-gauge needle has seemed to make bleeding following removal of the needle insignificant. Perhaps of equal importance to the increased safety and simplicity of the procedure is the fact that the atrial pressure pulse can be carried on the recorder for as long as desired without regard to the time that the instruments remain in the patient's tracheobronchial tree. In addition to this, the fact that the patient is in a comfortable position, without significant respiratory discomfort, breathing normally, makes the data obtained in this manner much more compatible with a resting physiologic state.

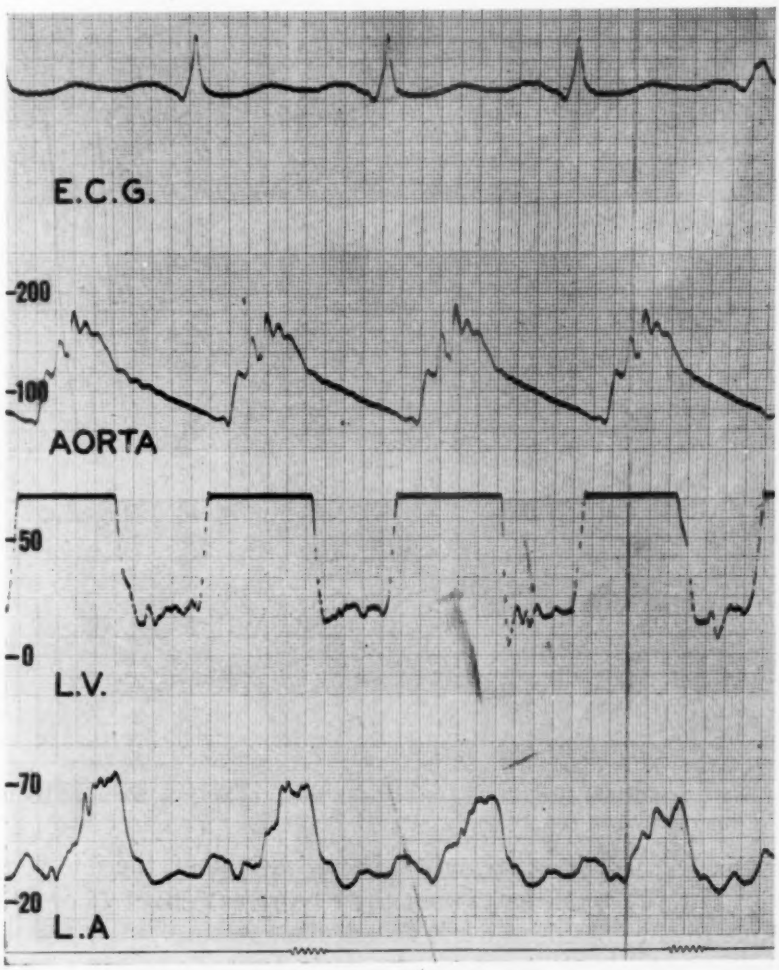

Fig. 3.—The aortic, ventricular diastolic, and left atrial pressure pulses in a case of severe mitral insufficiency. Note the undamped frequency response which can be obtained by these techniques.

Thirty-three percutaneous left ventricular punctures have been performed with only one other minor complication in addition to those listed in the preceding paragraph. The tracings obtained by this method have been satisfactory in all but two instances. In these two cases, excessive damping was a problem which could not be eliminated. In three other cases attempts at left ventricular puncture have failed because of either severely emphysematous configuration of the chest or nearly normal size of the heart. It is, of course, much simpler to carry out this procedure in patients with very large hearts. The additional complication was the production of a 20 per cent pneumothorax, which was noted three hours after the procedure, but which had corrected itself by the following day.

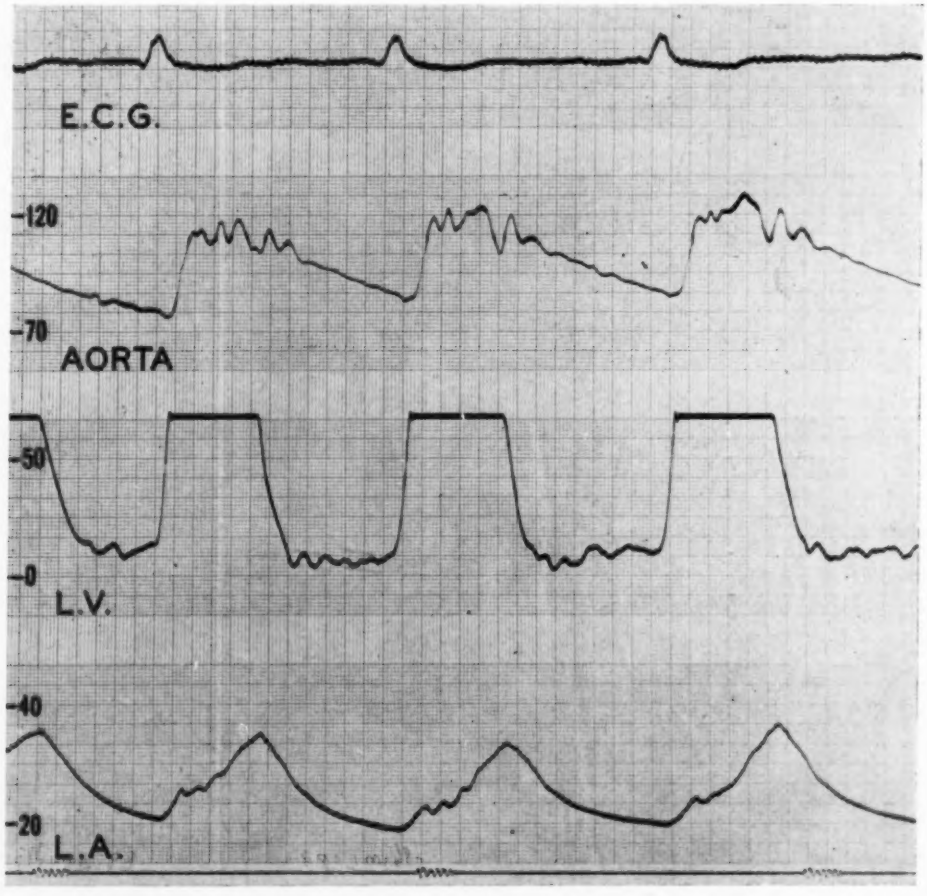

Fig. 4.—Aortic, left ventricular diastolic, and left atrial pressure pulses in a case of severe mitral stenosis.

Forty-six transaortic retrograde catheterizations of the left ventricle have been carried out. It is estimated that these represent about 75 or 80 per cent of the attempts to thus obtain the left ventricular pressure pulse. In this series of studies there has been one instance of ventricular tachycardia with momentary syncope of the patient. There have been no other significant complications. Additional material as well as details of the technique and of the results obtained

will be presented in a paper now being prepared by one of us (G. V.).[14] The cases, listed in Table I, in which retrograde left ventricular catheterization was carried out were, for the most part, cases of aortic stenosis.

Since using the new atrial puncture technique and the two techniques for left ventricular study, we have obtained all of the data sought in 69 out of a total of 78 combined procedures.

SUMMARY

A modified technique for left atrial puncture by the transbronchial route, which makes this approach even safer and more reliable, is presented. The results of various combinations of procedures for hemodynamic studies of the left heart are presented. The value of a versatile armamentarium of techniques for left heart puncture or catheterization is emphasized.

The studies reported in this paper have been performed in the Circulation Laboratory, Presbyterian Hospital, Philadelphia. The authors have comprised merely a part of the team which carries out these studies and therefore wish to acknowledge the active participation in this work of Drs. J. Dow, N.A.J. Hamer, R. Trout, B. Iaia, H. Gadboys, V. Shaver, and J. Pierce.

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Hemodynamic Studies in Acute Myocardial Infarction

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PREVIOUS INVESTIGATIONS

Hemodynamic studies in patients with acute myocardial infarction have been performed by various methods. In 1941, Grishman and Master,[1] using the method of Wezler and Boeger, determined the cardiac output in 5 cases; in 4 of these the cardiac output was found to be definitely reduced, especially on the second and third days after the onset of the illness. Ballistocardiographic studies by Starr and Wood[2] likewise revealed a subnormal cardiac output in cases of acute myocardial infarction, although normal values were also obtained. The cardiac catheter is not a suitable instrument for investigations during the acute phase of the disease, owing to the serious prognosis and, in particular, the possibility of sudden death. Injections of Evans blue dye and application of the Hamilton principle does, however, afford a method which may be employed at the bedside even with subjects who are seriously ill. In 1952, Freis and associates[3] carried out hemodynamic studies with this method in 11 cases of acute myocardial infarction and compared the results with those from normal and hypertensive cases. In the mild cases the cardiac output was within normal limits, but in the cases exhibiting shock it was abnormally low. The heart rate increased with the severity of the infarction. In the moderately severe and severe group the stroke volume was slightly reduced, while in the patients suffering from shock a marked reduction was found. The circulation time was prolonged in the more severe cases. The "central" blood volume was not significantly altered in any of the various groups. The total blood volume tended to be slightly reduced in the severe cases. The authors concluded that the depression in stroke volume was due to failure of the heart as a pump, and not to hypovolemia.

Smith, Wikler and Fox[4] studied the hemodynamics in acute myocardial infarction in 10 patients without shock, in 9 patients with shock, and in 12 patients during convalescence. Very low values for cardiac index were found in the shock cases, but the cardiac output was also subnormal in the cases without shock. Following recovery a significant increase of the cardiac index was noted, although the values were still lower than normal.

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Gilbert, Goldberg and Griffin[5] examined 20 patients during the initial phase of acute myocardial infarction. They found a lowering of the cardiac index and a prolongation of the circulation time roughly proportional to the clinical severity of the attack.

Gammil and associates[6] examined 39 cases of acute myocardial infarction within 67 hours of the onset of the disease. The mild cases had the highest values for cardiac output and stroke volume, and the lowest values for the appearance time of the dye. During hospitalization a significant increase in stroke volume and cardiac output was noted in those patients comprising the group of most serious cases. The values obtained in this group 4 weeks or more after the first examination equalled the values found in the group of less severe cases.

Recently, Lee[7] examined 11 patients with acute myocardial infarction on admission to hospital. In 9 of the subjects further studies were performed 4 to 9 weeks later. The cardiac output was lowest in the patients who were clinically most collapsed, but, on the whole, was less reduced here than in a group of patients with left ventricular heart failure not attributable to acute infarction. The cardiac output rose during recovery in 6 patients. In 1 patient no change was observed. In 2 subjects with few symptoms other than pain the cardiac output fell on recovery.

MATERIAL AND METHOD

The material comprised 35 subjects admitted to our department between November, 1956 and March, 1958, with a typical clinical picture of myocardial infarction. They were examined by the Evans-blue dilution technique shortly after admittance and again 3 to 4 weeks later. The first examination was carried out from 6 to 99 hours, on an average of 39 hours, after the clinical onset of the infarction. The second study did not cover 8 subjects who died during the interval.

The diagnosis was verified by electrocardiograms. Cases terminating fatally during the first few hours in hospital could, for practical reasons, not be examined. The routine treatment—administration of analgesics, anticoagulants, oxygen, and, on more specific indication, aminophylline, quinidine, or digitalis—was carried out independently of our examinations. The patients were encouraged to take part in nonstrenuous forms of activity at an early stage. If not suffering from shock or other serious conditions, they were generally moved from bed to a chair for increasing periods of time (15 to 30 minutes) from the second or third day in hospital, although only subsequent to the first examination.

The material has been grouped according to the clinical condition at the time of the first examination: *Group I*, uncomplicated cases with no clinical signs of hemodynamic disturbances; and *Group II*, severe cases with clinical signs of circulatory failure (pulmonary congestion, hypotension, tachycardia, and seriously affected general condition).

None of the subjects suffered from congestive heart failure prior to the infarction. It developed afterward in one individual, but only to a moderate degree, and all subjects were in good condition at the time of the second study.

The examinations were carried out with the subjects resting quietly in bed in the usual semirecumbent position. Oxygen was administered through a closed mask in order to avoid disturbances in the dye dilution curves from spontaneous fluctuations of the oxygen saturation of the blood. Approximately 20 mg. of Evans blue dye was injected in the course of 1 to 2 seconds through an antecubital vein, either directly or by means of a polyethylene catheter introduced from 5 to 10 cm. from the point of insertion. Continuous registration of the concentration of the dye was obtained by means of a photoelectric earpiece and a modified Coleman oximeter connected to an amplifier and with an electrocardiograph moving at a speed of 10 mm. per second (Broch and Haarstad[8]). For calibration of the dye dilution curve the concentration of dye in the blood was determined in a Unicam spectrophotometer, 10 minutes being allowed for com-

plete mixing. The distance between the preinjection level of the curve and the level recorded following complete mixing of the dye will correspond to the spectrophotometrically obtained dye concentration value. Determination of the dye concentration value represented by any point of the dilution curve is thus made feasible.

The special terms employed here in connection with the dye dilution curves are used in accordance with the definitions of Wood and Swan[9]: *AT:* Appearance time—the interval from the beginning of the injection of dye to the first appearance of the dye in the ear capillaries. *PT:* Passage time—the interval between the first appearance of the dye in the ear capillaries and the completion of the first passage of the dye through these vessels. The end point of this time interval has been determined graphically by extrapolation to zero of the descending limb of the dye concentration curve transferred to semilogarithmic paper. *ITBV:* The intrathoracic blood volume—signifying the volume in the circulatory system between the point of dye injection and the point of dye concentration recording, i.e., between the antecubital vein and the ear. *TBV:* The total blood volume.

The calculation of the cardiac output and ITBV was made according to the Hamilton principle.

Statistical Symbols.—The significance of the difference between two means and of the individual differences has been tested by Student's t-test. In the tables the significance level is given as follows:

*Denotes a significance of 5 per cent level ($P < 0.05$).
**Denotes a significance of 1 per cent level ($P < 0.01$).
***Denotes a significance of 0.1 per cent level ($P < 0.001$).

RESULTS

The results are given in Tables I through IV.

A comparison of the results in the 8 cases which terminated fatally with the results recorded at the first examination of the survivors discloses marked differences (Table I). In the fatal cases, high values for appearance time and passage time were recorded, indicating a general slowing up of the circulation. The change is especially marked in the average value for passage time, which in the fatal group was increased by 24 seconds. The average stroke volume of the subjects who died was 25 ml. less and the average cardiac output 2 liters per minute less than the corresponding value recorded at the first examination of the survivors. These differences are statistically significant. The average heart rate, however, was the same. Thus, the difference in the average cardiac output and the cardiac index depended on the alteration in the stroke volume. The average values for the intrathoracic blood volume and total blood volume were lowest in the fatal group, but the difference between the groups is small and not significant.

A corresponding difference on the first examination was found between Group I and Group II (Table II). The circulation was much slower, as demonstrated by a longer AT and PT, and the stroke volume and the cardiac output were reduced in the severe cases. The differences in these values between the groups are all significant. The average values for ITBV and TBV, on the other hand, are almost the same in the two groups.

A significant difference in cardiac output was found even between the dead and the survivors included in Group II (Table III).

The results obtained from comparison of the values of the first and the second examinations are given in Table IV.

TABLE I. AVERAGE CIRCULATORY DATA OF ALL CASES, SURVIVORS AND FATAL CASES, ON ADMISSION. COMPARISON OF SURVIVORS AND FATAL CASES

	NUMBER OF CASES	APPEARANCE TIME (SEC.)	PASSAGE TIME (SEC.)	CARDIAC OUTPUT (L./MIN.)	CARDIAC INDEX (L./MIN./M.^{2})	PULSE	STROKE VOLUME (ML.)	INTRA-THORACIC BLOOD VOLUME (L.)	TOTAL BLOOD VOLUME (L.)
Total Cases	35	17.5	61.8	4.63	2.56	84	56.9	2.68	4.70
Survivors	27	15.9	56.4	5.1	2.81	84	62.7	2.75	4.76
Dead	8	22.9	80.0	3.05	1.73	84	37.4	2.42	4.49
Difference between survivors and dead	—	7.0	23.6	2.05	1.08	0	25.3	0.33	0.27
Student's t-test	—	3.99***	1.94	3.67***	3.38**	—	2.9**	1.0	0.58

TABLE II. AVERAGE CIRCULATORY DATA OF GROUPS I AND II ON ADMISSION. COMPARISON OF THE GROUPS

	NUMBER OF CASES	APPEARANCE TIME (SEC.)	PASSAGE TIME (SEC.)	CARDIAC OUTPUT (L./MIN.)	CARDIAC INDEX (L./MIN./M.^{2})	PULSE	STROKE VOLUME (ML.)	INTRA-THORACIC BLOOD VOLUME (L.)	TOTAL BLOOD VOLUME (L.)
Group I	18	14.3	43.5	5.62	3.03	83	69.9	2.60	4.63
Group II	17	20.9	81.1	3.59	2.04	86	43.1	2.76	4.78
Difference	—	−6.6	−37.6	2.03	1.01	−3	26.8	−0.16	−0.15
Student's t-test	—	4.78***	4.38***	4.52***	3.71***	—	3.95***	—	—

The asterisks in Tables I and II denote the significance level.

TABLE III. AVERAGE CIRCULATORY DATA OF THE SURVIVORS OF GROUP II. COMPARISON OF GROUP II SURVIVORS AND FATAL CASES ON ADMISSION

	NUMBER OF CASES	APPEARANCE TIME (SEC.)	PASSAGE TIME (SEC.)	CARDIAC OUTPUT (L./MIN.)	CARDIAC INDEX (L./MIN./M.^{2})	PULSE	STROKE VOLUME (ML.)	INTRA-THORACIC BLOOD VOLUME (L.)	TOTAL BLOOD VOLUME (L.)
Survivors	9	19.1	82.1	4.07	2.36	87	48.2	3.05	5.03
Dead	8	22.9	80	3.05	1.73	84	37.4	2.42	4.49
Difference	—	3.8	2.1	1.02	0.63	3	10.8	0.63	0.54
Student's t-test	—	1.56	—	2.32*	2.41*	—	1.68	1.74	—

Significance level denoted by asterisks.

TABLE IV. COMPARISON BETWEEN THE FIRST AND SECOND EXAMINATIONS OF GROUP I AND GROUP II

		NUMBER OF CASES	APPEAR-ANCE TIME (SEC.)	PASSAGE TIME (SEC.)	CARDIAC OUTPUT (L./MIN.)	CARDIAC INDEX (L./MIN./M.^{2})	PULSE	STROKE VOLUME (ML.)	INTRA-THORACIC BLOOD VOLUME (L.)	TOTAL BLOOD VOLUME (L.)
Group I	Difference between first and second examinations	18	1.23	0.22	−0.38	−0.2	5	−7.2	−0.08	−0.14
	Student's t-test	—	1.5	0.07	0.82	0.84	1.18	1.3	0.31	0.43
Group II	Difference between first and second examinations	9	3.4	29.1	−1.5	−0.86	5	−22.0	0.19	0.74
	Student's t-test	—	1.77	1.6	1.74	1.72	0.98	2.17	0.65	2.1

The hemodynamic conditions in Group I were practically the same on the first and second occasions, only small and statistically insignificant differences being noted. The survivors in Group II showed more marked changes. Fig. 1 shows the results in a typical case.

The values for AT, PT, and heart rate were lower on the second occasion. At the same time, the average stroke volume and cardiac output were found to be increased by 22 ml. and 1.5 liters per minute, respectively. There was a slight increase in the ITBV and the TBV. None of the differences, however, is statistically significant.

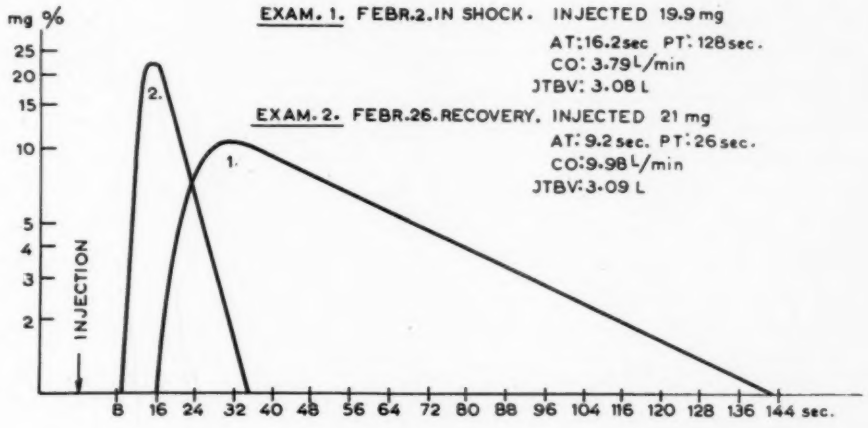

Fig. 1.—Dye dilution curves in a case of severe myocardial infarction shortly after onset (*1*) and 24 days later (*2*).

DISCUSSION

Our average values for stroke volume, cardiac output, and circulatory velocity indicate a definite reduction in the performance of the heart during the acute phase of myocardial infarction. The deviations from the normal are, however, attributable to the results from a specific group of the cases. In most subjects the results obtained show little change between the first and second examination.[5]

Thus we found no definite indication of reduced circulation during the acute phase in Group I, which comprised almost half of the material. The slight changes found in AT, stroke volume, and heart rate between the first and second examinations are statistically insignificant. The values for cardiac output in Group I are nearly identical at the two examinations. Although the subjects included in the group showed no clinical signs of circulatory failure, several of them were visibly affected by the illness and had severe pain, increased temperature, leukocytosis, and marked electrocardiographic changes.

Our findings are in accordance with the results of other workers.[2,6] However, some authors[4] have also reported subnormal values for cardiac output during the acute phase of myocardial infarction in cases without initial shock, and a significant increase in the cardiac output at examinations undertaken from 6 to 8 weeks and up to 13 months following the acute stage of the illness. Owing to

the difference in interval between the first and second examinations, any comparison between their findings and ours on the second occasion must be treated with reserve. Since the main difference in the result is caused by the findings made at the first examinations, the unequal time interval can scarcely explain the discrepancy.

Definite hemodynamic changes, however, were found in the group in which low blood pressure, congestion of the lungs, and other signs of left ventricular failure gave clear clinical evidence of a grave circulatory disturbance. A marked reduction in stroke volume, unaccompanied by any great change in the pulse rate, is characteristic of these cases, and explains the low cardiac output.

The lowest values for stroke volume and cardiac output were found in the fatal cases. In these 8 subjects the average cardiac output was 3 liters per minute, but the pulse rate was not raised and the circulatory velocity was only slightly prolonged in comparison with those in the surviving members of the group who exhibited clinical signs of acute circulatory failure.

During convalescence a normalization of stroke volume, cardiac output, and circulation time occurred in the 9 survivors in Group II. Although the results at the second examination of these cases still compares unfavorably with the corresponding values obtained in Group I, the differences are not great. They would be smaller still but for the findings in a single subject in Group II who developed chronic heart failure during the interval between the examinations. In this subject the circulation time increased and the stroke volume and the cardiac output fell considerably between the first and second examinations.

On the whole, the changes in blood volume are small. The difference between the average intrathoracic blood volume and the average total blood volume of Group I and Group II is negligible. The difference within Group II of both ITBV and TBV between the fatal cases and the survivors is noteworthy, although not statistically significant. Similar findings have been obtained by other authors.[2,3]

Reduced blood volume values during the acute phase are most easily explained by hemoconcentration. The hematocrit readings in our series are in accordance with this view. The fatal cases showed an average hematocrit value of 47.6 per cent, while the corresponding value in the 9 survivors in Group II was 44.7 per cent on the first examination.

SUMMARY

Hemodynamic determinations with the dye dilution technique were carried out in 35 cases of acute myocardial infarction during the first phase of the disease. Approximately 3 weeks later the 27 patients who were still alive were re-examined in the same way.

On the whole, the circulatory conditions in the 18 mild or moderately severe cases did not vary much between the first and the second examinations and were within normal limits.

In the group of severe cases (17 patients) the first examination showed a marked reduction of the cardiac output and the stroke volume, while the appear-

ance time and the passage time were prolonged. Comparison with the corresponding values of the mild or moderately severe cases on admission yielded statistically significant differences. Comparison of the values from the 8 fatal cases with those obtained on the first occasion in the 9 survivors belonging to the severe group showed a statistically significant difference in the cardiac output. Comparison between the values from the first and the second examination in the 9 survivors of the severe group disclosed a definite trend toward normalization, although not to a statistically significant degree.

A comparison of the various categories of cases on admission revealed small differences only in the values for total blood volume and intrathoracic blood volume. Likewise, comparison of the results of the first and second examinations showed small changes in these values.

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Experimental and Laboratory Reports

Angina Pectoris. II. Observations on the Classic Form of Angina Pectoris (Preliminary Report)

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Although almost two centuries have elapsed since Heberden's classic description of angina pectoris, a number of questions have remained. Many important clinical, electrocardiographic, experimental, and other aspects of angina pectoris are difficult to understand. It appears that the problem of angina pectoris as presented in medical school or reported in the literature is oversimplified. The many differences between classic angina pectoris and a variant form of the disease need explanation. This preliminary report, although dealing primarily with the nature of classic angina pectoris itself, deals also with the reason for the remarkable differences between classic angina pectoris and the variant form of this disease.[1]

The direct experimental approach to the beating hearts of patients with angina has been virtually impossible in the past. Direct exploration of the human heart has been feasible and justifiable only relatively recently with the advent of surgical procedures for the treatment of arteriosclerotic heart disease. Direct epicardial electrocardiography in such patients with angina pectoris, to our knowledge, has not been reported heretofore. The location of areas with epicardial S-T segment depressions in such human hearts has been different from

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what has been anticipated. This new knowledge of the distribution of areas with epicardial S-T depression in human patients with angina has made possible another experimental approach to a condition resembling angina, electrocardiographically, in animals. Since S-T depression is so important in clinical angina pectoris, further light on its pathogenesis is considered in this and succeeding articles.

I. THE DIRECT EPICARDIAL ELECTROCARDIOGRAM IN HUMAN ANGINA PECTORIS

Observations.—An opportunity was afforded for direct epicardial exploration in 15 patients with arteriosclerotic heart disease and severe angina pectoris who underwent the Beck procedure. Immediately after the opening of the pericardium and its separation from the epicardium, the anterior, posterior, and lateral epicardial surfaces of both ventricles were explored systematically with small, saline-soaked, cotton-tipped electrodes.

Multiple areas, or "islands," registering significant S-T segment depressions were found scattered over all surfaces of *both* ventricles in all 15 patients (Fig. 1). The S-T segments were isoelectric between these "islands" with S-T segment depression. S-T segment elevation was found only in areas of old myocardial infarction in 5 patients, and in areas injured by separation of old pericardial-epicardial adhesions.

The "islands" showing S-T segment depression could not be distinguished visually from other epicardial areas with isoelectric S-T segments. The "islands" with S-T segment depression *did not show cyanosis or pallor.*

Arrhythmias during surgery were infrequent in both the group with angina and the control group, except during intubation or direct irritation of the myocardium.

Direct epicardial electrocardiograms were recorded in several control patients undergoing chest surgery for other than cardiac reasons. In these patients, "islands" showing S-T segment depression were not found over the epicardial surface except if the patients were obviously anoxic.

Discussion.—The anginal syndrome was severe in all of these patients, with attacks being provoked by even the slightest effort or excitement. The diverse stresses of the complex surgical procedure would seem to be at least of comparable magnitude. The well-known occurrence of myocardial infarction with surgery in occasional patients is probably related to some of the changes induced by surgery. On this basis the electrocardiographic findings recorded during surgery would seem similar to those recorded during an anginal attack.

The finding of widely disseminated areas with S-T segment depression in all 15 patients indicates that attacks of angina are due to a *generalized* disorder of the heart involving diffuse areas in both ventricles.

The only typical ECG finding during an attack of angina pectoris is depression of the S-T segment in standard leads I, II, and III, and in the left precordial leads. The absence of reciprocal S-T elevations in standard leads has puzzled students of electrocardiography since the question first was raised by Wilson and Johnston.[2]

The finding of S-T depression only in classic angina pectoris, in the standard leads of the ECG, is explained by the diffuse distribution of these "islands" of S-T depression as recorded at the epicardial surface.

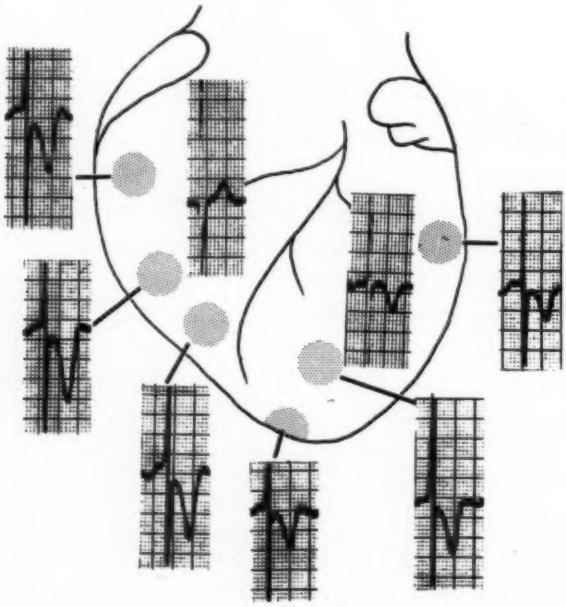

Fig. 1.—Direct epicardial leads in a patient with severe classic angina pectoris obtained at time of cardiac surgery. Multiple "islands" of S-T segment depression, diagrammatically represented, are located over all aspects of both ventricles. The S-T segments are isoelectric between these "islands" of S-T depression. The appearance of the myocardium over these "islands" does not differ from that of the surrounding myocardium.

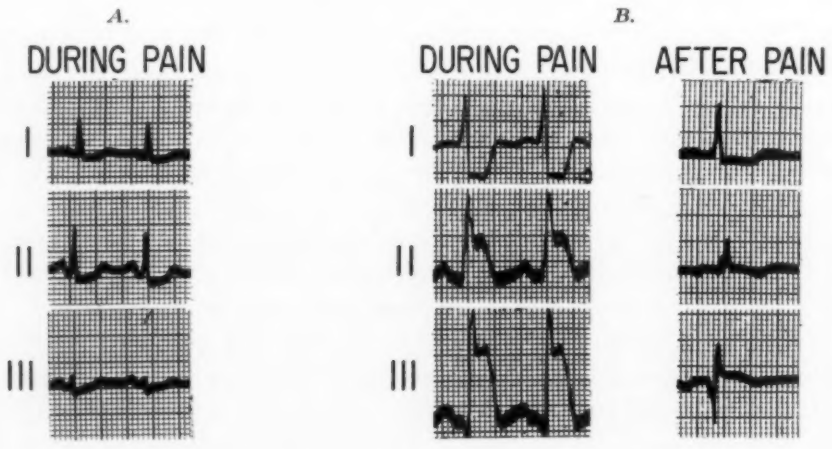

Fig. 2.—*A*, Classic angina pectoris: S-T segments show depression without reciprocal S-T elevation. ECG obtained after exercise. *B*, Variant form of angina pectoris: During spontaneous pain, S-T segments show elevation in Leads II and III, with reciprocal S-T depression in Lead I. Immediately after pain, the ECG returns to normal or to the prepain pattern. (Courtesy of American Journal of Medicine.[1])

The absence of reciprocal S-T elevations in standard leads also is clarified. Since the areas of primary S-T depression are located all over both ventricles, no reciprocal S-T elevation is manifest in the standard leads. This situation is opposite, in a way, but analogous to that prevailing in acute diffuse pericarditis, in which S-T elevations are registered in the absence of reciprocal S-T depressions in standard leads.

In the variant form of angina pectoris,[1] in contrast to classic angina pectoris, reciprocal S-T changes are characteristic (Fig. 2). In the variant form of angina pectoris the primary S-T elevation is localized to a large discrete area supplied by a single major coronary artery or one of its larger branches (Fig. 3). Distinct

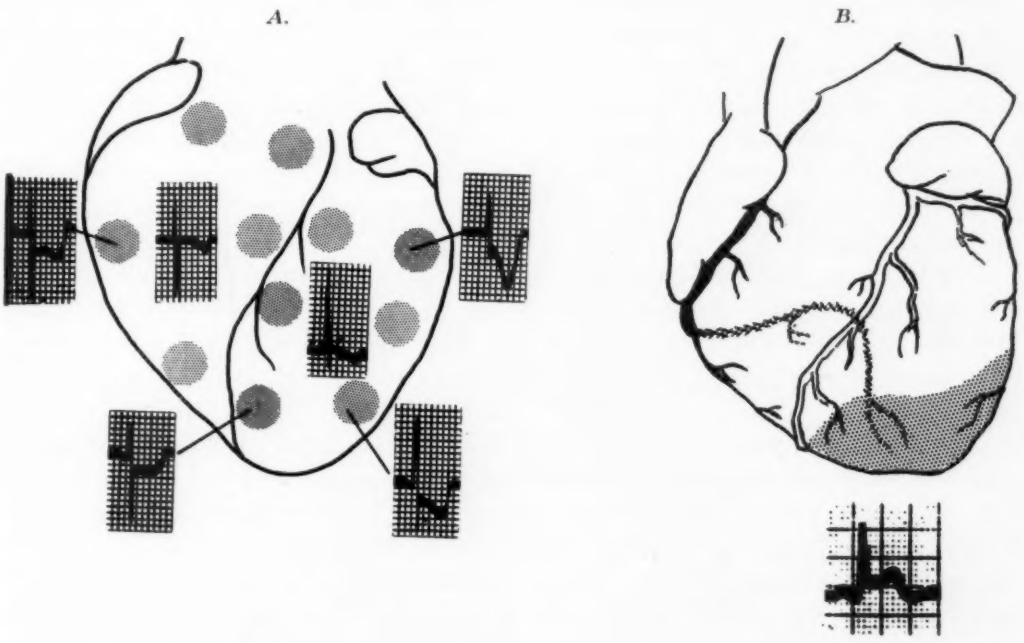

Fig. 3.—Distribution of S-T changes in angina pectoris. *A*, **In classic angina pectoris, multiple "islands" of S-T segment depression are scattered over both ventricles.** *B*, **In the variant form of angina, S-T segment elevation is localized to a large discrete area supplied by a large coronary artery.**

reciprocal S-T depressions which are identical to those of acute myocardial infarction are recorded in standard leads. The S-T elevations and reciprocal depressions are prominent but disappear completely in a few minutes. This does not imply that the pathologic process in the variant form of angina pectoris is not generalized. It is probable that the pathologist will not be able to distinguish between hearts with these two forms of angina, just as he finds it difficult to correlate atherosclerosis in any one heart with the degree or even the presence of angina.

The site of origin of the pain in classic angina has been long a debated question. It would seem likely that the pain may arise in at least some of these diffuse "islands" with S-T segment depression.

II. EXPERIMENTAL PRODUCTION OF CERTAIN FEATURES OF ANGINA PECTORIS

Hypotension from any cause may be associated with the development or exacerbation of angina pectoris in patients with coronary artery disease. A hypotensive episode may be associated with the initial attack of angina. During anginal attacks transient S-T segment depressions usually are recorded in the electrocardiogram. Therefore, the effect of the hypotensive state on the electrocardiogram of dogs was investigated in order to determine whether phenomena similar to those in human angina pectoris occurred.

Observations in a Condition Simulating Classic Angina.—The heart was exposed in 18 dogs, and control electrocardiograms were obtained from multiple epicardial areas on the anterior, lateral, and posterior surfaces of both ventricles, as well as from the left ventricular cavity and subendocardium. Hypotension then was produced in each dog by slow bleeding from the femoral artery until the systolic pressure fell to about 40 mm. Hg. Electrocardiographic exploration then was repeated with the blood pressure being maintained at this level.

Electrocardiograms recorded at the epicardium showed multiple diffuse "islands" of S-T depression. These "islands" of S-T depression were recorded over all epicardial surfaces, and were interspersed with areas of isoelectric S-T segments (Fig. 4).

The areas with S-T depression could not be distinguished visually either by cyanosis, pallor, or other gross changes from areas with isoelectric S-T segments. Elevation of the blood pressure, either spontaneously or by transfusion, was associated with the prompt disappearance of these "islands" of S-T depression.

Arrhythmias were observed rarely during these experiments, except for the *sudden appearance of ventricular fibrillation as a terminal event.*

Comment.—These multiple diffuse "islands" of S-T segment depression occurring during hypotension in the dogs were identical with those found in human patients with angina pectoris. These "islands" of S-T depression were diffusely scattered over all epicardial surfaces in both the experimental animal and the human patient. Visual identification of these areas with S-T depression was not possible either in the experimental animal or in the human patient. The similarity of the ECG changes in human angina pectoris and in that produced by the hypotension in animals suggests that hypotension may provide an experimental basis for the further study of angina pectoris. It is not assumed that angina pectoris was produced in these animals. It is quite conceivable, however, that the experimental situation which resulted simulated that which occurs in patients with angina pectoris with diffuse coronary artery disease and partially obstructed coronary arteries. In such patients the blood pressure at the proximal end of the coronary arteries may be normal, but because of the partially constricted lumen the pressure distally in these arteries may be very low. Thus, the pressure in the distal coronary arteries in patients with angina pectoris may be comparable to that in the hypotensive dog. The low distal pressure of the coronary artery may not be associated with angina and ECG changes at rest, partly because of compensatory vasodilatation peripheral to such hypotensive regions. With increase in the work of the heart, however, angina and S-T segment depression are likely to occur.

This may be explained on the basis of the peripheral vasodilatation already present at rest. With exercise and increase in the work of the heart, further vasodilatation in the peripheral vessels may be only very little, if at all, beyond that already present at rest. Thus, electrocardiographic changes and pain may occur with exercise.

The widespread diffuse location of the "islands" of S-T segment depression in classic angina makes it understandable why this form of angina only rarely disappears following myocardial infarction, except following the development of auricular fibrillation, heart failure, or with marked limitation of activity. The persistence of angina following myocardial infarction was noted in all 15 patients in this series who underwent the Beck procedure, for all had a myocardial infarction with persistent or even more severe angina subsequent to the infarction.

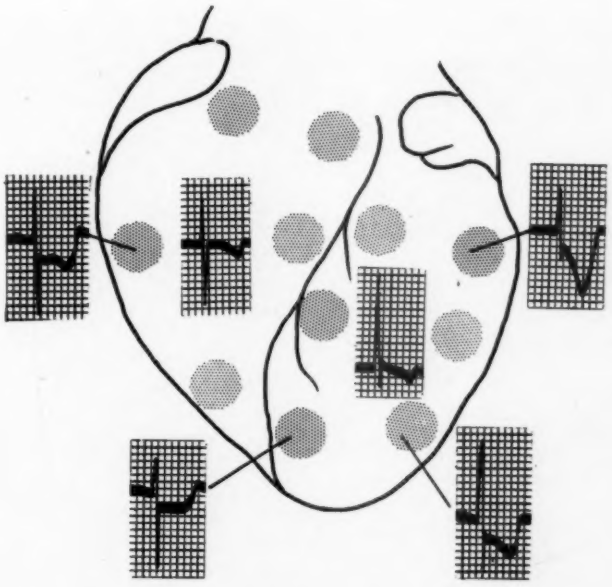

Fig. 4.—Direct epicardial leads in a dog with severe hypotension. Numerous "islands" of S-T depression, diagrammatically represented, are found over all aspects of the epicardial surface of both ventricles. Between these "islands" the S-T segments are isoelectric. The "islands" of S-T depression do not differ visually from surrounding areas. The S-T depressions appear identical to those found in patients with angina pectoris (Fig. 1).

Increase in severity of the angina following infarction is understandable, for the remaining noninfarcted myocardium may be called on to do a greater share of the work. Because of the widespread character of the disorder in classic angina, infarction of a single large area still leaves other areas which may give rise to pain.

The disappearance of the variant form of angina following myocardial infarction is explained, also, for when infarction occurs here it does so in the single area which previously caused pain and S-T change. Thus, infarction of this single area is followed by disappearance of the variant type of pain.

The occurrence of S-T segment elevation during anginal pain of the variant type makes prediction possible as to the site of future myocardial infarction.

In the variant form of angina the area with S-T segment elevation is the likely site of future myocardial infarction, but in the classic form of angina, prediction of the site of future myocardial infarction usually is not possible.

Epicardial cyanosis occurs when a single large coronary artery is obstructed, as has been described previously.[1] The area showing cyanosis is the same as that showing S-T segment elevation. This cyanotic area is restricted to the distribution of the coronary artery which is obstructed. In patients with angina pectoris and in dogs with hypotension, cyanosis has not been observed in areas with S-T segment deviation.

The electrocardiographic and visual findings in the experimentally simulated form of variant angina suggest that temporary hypertonus of the single large sclerotic artery may be responsible for the attacks in patients.[1] Hypertonus

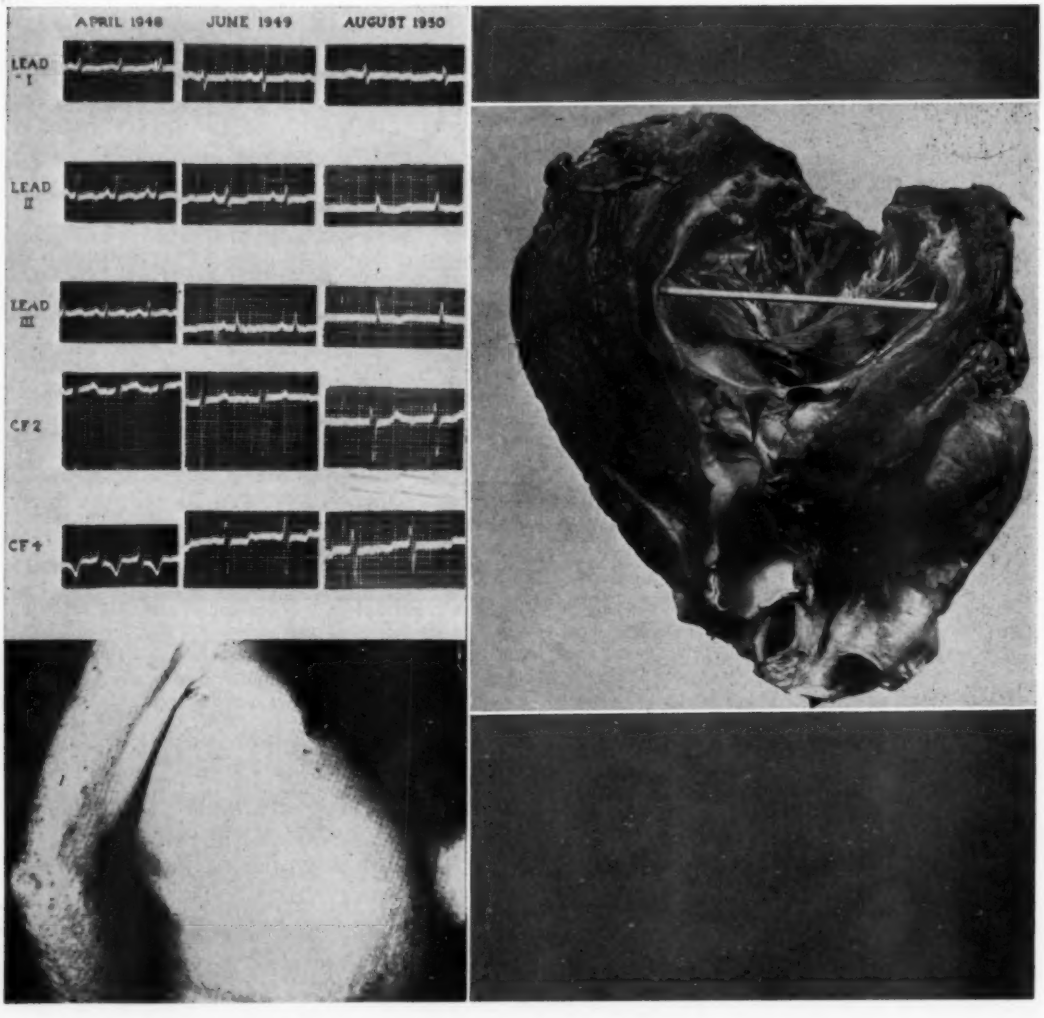

Fig. 5.—Patient with subendocardial fibroelastosis. The patient was in heart failure preceding death. Autopsy showed marked subendocardial fibroelastosis. Electrocardiograms prior to death did not show S-T segment depression. (Courtesy of S. G. Blount, Jr.)

of the coronary arteries would not seem, however, to be etiologically significant in classic angina. If even slight hypertonus occurred in the already narrowed coronary arteries of patients with classic angina, cyanosis of such areas would be expected. This has not been observed in any of the 15 patients studied to date. If arterial hypertonus was responsible for each area of S-T depression in classic angina, it would have to be of a very widespread nature to account for the widespread location of these changes. Under such circumstances a fatal outcome to most anginal attacks might be expected. This does not imply that increased arterial tonus never occurs in classic angina pectoris, for there are reasons to believe that it may with cold, visceral disease, etc., but indicates rather that widespread coronary artery hypertonus is not the usual cause.

Arrhythmias occurred frequently in the clinical and simulated variant form of angina, but less commonly in the clinical or simulated classic form, except as a terminal event. Ventricular fibrillation appearing abruptly was observed

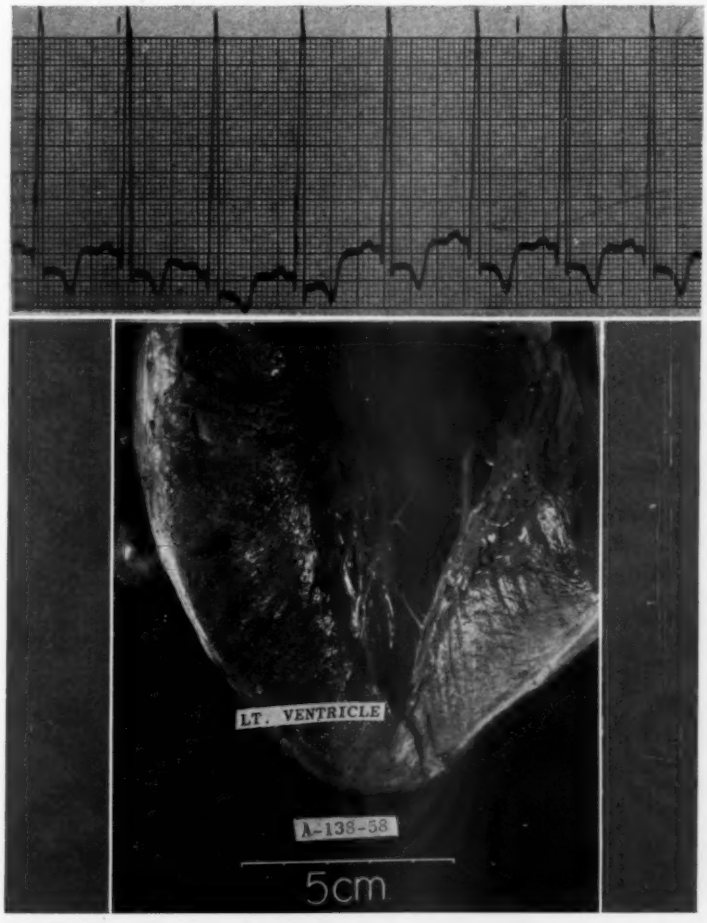

Fig. 6.—S-T depression with idiopathic hypertrophy of the heart. The S-T segment is markedly depressed (Lead V_6). The endocardium and subendocardium are not diseased disproportionately to the remainder of the heart. (Photograph of the heart, courtesy of Dr. Lewis Lichtenstein, Veterans Administration Hospital, Los Angeles.)

as a terminal event in at least 25 of the dogs. The abrupt occurrence of this fatal arrhythmia, without other preceding lower arrhythmias, may account for many of the sudden deaths which are seen in patients with angina pectoris who rarely complain or extrasystoles or tachycardia before death. By contrast, the variant form of angina pectoris is commonly associated with other lower arrhythmias, such as ventricular extrasystoles and tachycardia. These arrhythmias in the variant form of angina usually occur after the pain has been present and has increased to a certain intensity.

In addition to these differences between classic angina pectoris and its variant form, there appear to be fundamental chemical differences which are discernible during attacks. These chemical findings in the two types of angina pectoris will be presented in another paper.[7]

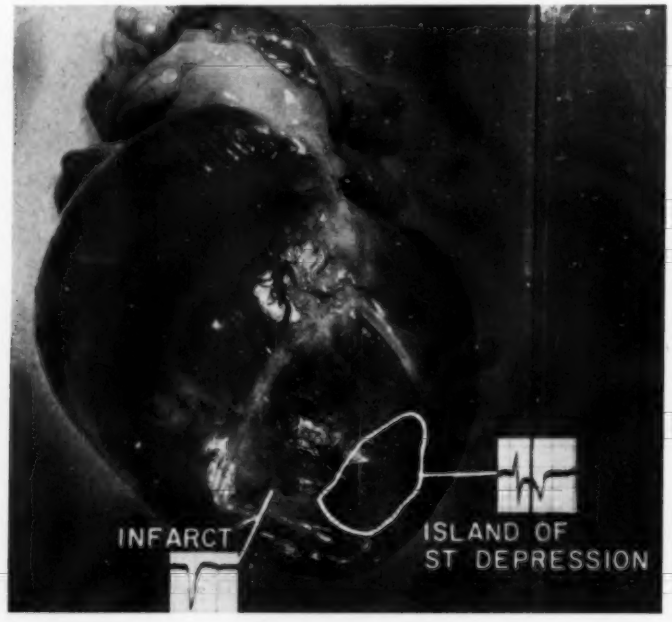

Fig. 7.—Three-month-old infarct in dog. There is a large area adjacent to the infarct wherein S-T depression is recorded at the epicardium. A simultaneous subendocardial electrocardiogram from this area showed no change in the S-T segment. Similar findings have been seen in patients with coronary artery disease.

III. THE ORIGIN OF S-T SEGMENT DEPRESSION

A. *Clinical Considerations.*—Classic theory states that S-T segment depression recorded at the epicardium is due to injury of the subendocardium. Thus, the S-T segment depression characteristic of angina pectoris would be attributed to changes in the subendocardium. There are a number of clinical situations, however, in which S-T depression is not explainable on this basis. (1) Patients with subendocardial fibroelastosis often have electrocardiograms with normal S-T segments. Although this disease severely affects the endocardium and subendocardium, the lesion appears to create no consistent S-T

deviation (Fig. 5).[3] (2) In some instances of myocardial infarction, S-T depression rather than elevation occurs.[4] According to classic theory, such an infarction should be limited to the subendocardium and not involve the more superficial layers. Such subendocardial infarcts without some extension either anatomically or chemically to the outer layers would appear, in all probability, to be quite rare. (3) In some patients with chronic pericarditis, S-T depression may occur. Even though only a thin shell of subepicardial tissue is diseased, S-T depressions are recorded.[5] (4) In conditions classified as "idiopathic hypertrophy of the heart," S-T segment depressions often are found (Fig. 6). The endocardium and subendocardium of these hearts, however, are not diseased disproportionately to the remainder of the heart.

In view of this clinical evidence in opposition to the classic theory that S-T segment depression originates in the subendocardium, an experimental investigation of this problem was undertaken. Results of some of these studies are presented below.

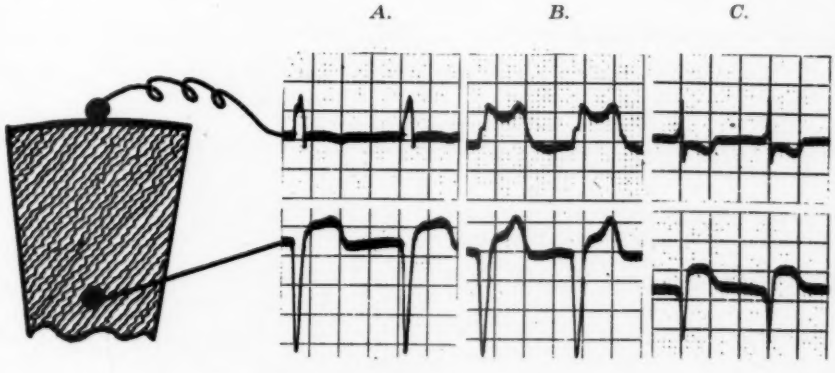

Fig. 8.—Direct surface and subendocardial leads from an infarcted region before and after tying a branch of the anterior descending coronary artery. *A*, Control. *B*, Three minutes after the tie. The injury effect is marked at the surface but very slight in the subendocardium. *C*, One hour later. The injury effect has disappeared and the surface S-T segment has become depressed.

B. *Experimental Evidence for the Subepicardial Origin of S-T Segment Depression.*—

1. *S-T segment changes with hypotension:* As described earlier, "islands" of epicardial S-T depression were produced in 18 dogs by bleeding until marked hypotension occurred. Simultaneous electrocardiograms then were recorded over the epicardial "islands" and from the underlying subendocardium and ventricular cavity. Despite the appearance of S-T segment depression over the epicardium, either an insignificant change or no change in the S-T segment was recorded from the underlying subendocardium or ventricular cavity in 17 of the 18 dogs.

2. *S-T segment changes with coronary artery ligation:* In 37 dogs a branch of the anterior descending coronary artery was ligated. One to four weeks later the pericardium was reopened. Simultaneous electrocardiograms were recorded at an epicardial area adjoining the area of the infarct (a "juxtainfarcted area") and from its underlying subendocardium (Fig. 7). The epicardial electrocardio-

TABLE I. SUMMARY OF VARIANT AND CLASSIC FORMS OF ANGINA PECTORIS*

VARIANT FORM OF ANGINA PECTORIS	CLASSIC FORM OF ANGINA PECTORIS
Clinical Differences	
1. Pain is not brought on by increased cardiac work	Pain usually is brought on by increased cardiac work
2. Emotional upsets do not provoke attacks	Emotional upsets often provoke attacks
3. Pain is usually more severe and of longer duration than in classic form of angina	Pain usually is less severe and of shorter duration than in variant form
4. Pain often waxes and wanes in cyclic fashion, forming a sine wave pattern in some cases. The pain peaks occur with remarkable regularity	Pain is not cyclical
5. The waxing and waning periods of attacks often are of equal duration	The waning periods of attacks generally are shorter than the waxing periods
6. Pain often occurs at about the same time each day	Pain does not occur as regularly each day unless related to exercise or emotion
7. Pain is not relieved by rest	Pain is relieved by rest
8. Anginal pain usually disappears immediately and dramatically after infarction	Infarction has no consistent effect on angina
9. Arrhythmias, often ventricular, occur during attacks in about 50 per cent of cases	Arrhythmias are not so common
10. Clinical diagnosis requires careful study	Clinical diagnosis usually is more obvious because of familiarity of syndrome
ECG Differences	
11. S-T segments are elevated transiently and often remarkably during the attack. Reciprocal S-T depression occurs in standard leads. The onset of a severe attack, or a mild attack may show no ECG changes	S-T segments generally show depression during the pain. Reciprocal S-T elevation is not observed in standard leads
12. S-T and T-wave changes occasionally, spuriously, may seem to improve a previously abnormal ECG	Spurious electrocardiographic improvement does not occur
13. Areas of myocardium which give rise to S-T elevation during attacks correspond to the distribution of a large coronary artery	Areas of myocardium which give rise to S-T depression are diffuse and do not correspond to the distribution of any single large coronary artery
14. Exercise test is of little value in diagnosis	Exercise test may be extremely valuable in diagnosis
15. Areas of the heart giving rise to S-T segment elevation are the sites of future infarction. This is the only situation wherein the site of future infarction can be predicted	Sites of future infarction are unpredictable
16. The QRS complex of the ECG frequently is affected during the severe attack. The R wave may become taller and broader or temporarily disappear	The QRS complex usually is unaffected by the attack

gram from the juxtainfarcted area showed S-T segment depression, but the subendocardial electrocardiogram showed no change in the S-T segment.

In 15 of these dogs the main coronary artery supplying the juxtainfarcted area then was ligated. Prior to ligation of this artery the juxtainfarcted area was characterized by epicardial S-T segment depressions. Upon ligation of this artery, however, the epicardial S-T segment depression was replaced by S-T segment elevation. Despite this change in epicardial S-T segment, no shift was recorded in the subendocardial S-T segment.*

Similar observations have been made in patients with previous coronary occlusion and S-T segment depression. Following a second coronary occlusion the previously depressed S-T segments have been replaced by elevated S-T segments.

These animal experiments indicate that S-T segment depression originates in the outer myocardial layers and not in the subendocardium (Fig. 8).

IV. CLINICAL SIGNIFICANCE

These animal experiments and clinical observations confirm earlier evidence from this and other laboratories,[6] indicating that S-T segment depressions are due

TABLE I—CONT'D

VARIANT FORM OF ANGINA PECTORIS	CLASSIC FORM OF ANGINA PECTORIS
Physiologic and Chemical Differences	
17. Attacks probably are due to transient increased tonus of a large narrowed coronary artery	There is no evidence of significant arterial hypertonus during attacks in most instances
18. Physiologic myocardial disturbance produces chemical changes of unknown nature	Physiologic and chemical disturbances probably are different from those in the variant form
Treatment	
19. Preliminary observations suggest that attacks may be prevented by nylidrin hydrochloride	Nylidrin hydrochloride generally is contraindicated and may precipitate attacks
20. Anticoagulants appear to be indicated in the variant form	There is a difference of opinion as to the efficacy of anticoagulants
Similarities	
21. The sex, age, and occupational distribution are similar. During the peaks, pain is identical in both conditions. Nitroglycerin promptly relieves the pain in both. Long-acting nitrites are prophylactic. Coronary artery disease is present. Myocardial infarction occurs frequently.	

*Summary of the present report and two others.[1,7]

*We wish to express our gratitude to Dr. R. Massumi, Dr. Louis Rakita, and Dr. Lois Schwartz for their assistance in these experiments.

to disturbances in the outer myocardial layers. Contrary to classic theory, the subendocardium does not contribute significantly to epicardial S-T deviations. Reciprocal S-T segment changes probably are too small to be readily demonstrated.[7] This conclusion is in agreement with well-established electrophysiologic theory.*

The differences and similarities between classic angina pectoris and the variant form are summarized in Table I.

SUMMARY

1. Surgical procedures for the treatment of arteriosclerotic heart disease has made the recording of direct epicardial electrocardiograms possible in 15 patients with severe classic angina pectoris. Numerous "islands" of S-T segment depression widely scattered over all epicardial surfaces of both ventricles have been demonstrated. Areas other than these "islands" showed isoelectric S-T segments. "Islands" with epicardial S-T depression were not found in control patients.

2. The "islands" with S-T segment depression could not be distinguished by virtue of pallor or cyanosis from the areas with isoelectric S-T segments.

3. The occurrence of S-T segment depression in standard leads in classic angina is explained by the diffuse distribution of these "islands" of S-T segment depression. Standard leads face the "islands" of depression.

4. The absence of reciprocal S-T segment elevation in other standard leads in classic angina is also explained. Reciprocal S-T elevation in standard leads is not manifest since the primary areas of S-T depression are located all over the ventricles. The occurrence of primary S-T segment elevation in the variant form of angina is noted, together with its restriction to a large discrete area supplied by a large coronary artery. In the variant form of angina the S-T segment depression is reciprocal in nature, in contrast to classic angina pectoris, in which reciprocal S-T segment changes are not noted in standard leads.

5. Diffuse "islands" of epicardial S-T segment depression were produced experimentally in dogs by bleeding to markedly hypotensive levels. These "islands" of S-T segment depression in dogs could not be distinguished visually from areas with isoelectric S-T segments. Similar findings were noted in human beings with angina pectoris.

6. Ligation of a large branch of the anterior descending coronary artery in dogs produced a large discrete area in which only epicardial S-T segment elevation was recorded. This area with S-T elevation was distinctly cyanotic, in contrast to the previously described "islands" with S-T depression which were not visually distinguishable. These findings were similar to those in patients with the variant form of angina pectoris.

7. The similarity of local hypotension at the distal end of partially constricted coronary arteries, to generalized hypotension in the presence of normal coronary arteries is noted.

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*A mathematical presentation of this theory of S-T depression will be included in a forthcoming article.

8. The frequent persistence of classic angina following a myocardial infarction is explained by the diffuse location of the "islands" with S-T depression. Following infarction, many such "islands" remain. The disappearance of the variant form of angina following a myocardial infarction also is explained as being due to the localization of the changes to the single area which has been infarcted.

9. The occurrence of S-T elevation in the variant form of angina makes prediction of the site of future infarction possible. The occurrence of S-T depression in classic angina does not permit prediction of the site of future infarction.

10. The appearance of epicardial cyanosis in areas with S-T segment elevation on temporary ligation of a coronary artery suggests that coronary artery hypertonus may precipitate the variant form of angina with its S-T segment elevation. The absence of epicardial cyanosis in patients with classic angina, and in dogs with hypotension, suggests that coronary artery hypertonus is not the usual cause of classic angina.

11. Ventricular arrhythmias are noted frequently in the clinical and simulated variant form of angina. They occur after the pain has been present awhile and has risen to a certain intensity. Arrhythmias are rare in the simulated form of classic angina, except for terminal ventricular fibrillation. Sudden deaths in classic angina probably occur as a result of ventricular fibrillation developing suddenly.

12. Several clinical conditions are presented in which S-T segment depression is found in the absence of changes limited to the subendocardium. A number of experiments are presented indicating that the subendocardium does not contribute in significant degree to S-T segment deviations. These experiments indicate that S-T segment depressions are due to disturbances in the outer myocardial layers.

13. The marked difference between S-T changes in classic angina pectoris (with S-T depression) and those in the variant form of angina or early myocardial infarction (with S-T elevation) suggests different chemical changes within the myocardium.[7]

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Stenosis in a Deformable Tube Inhibited by Outlet Pressure

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Previous studies have inquired into the effect of mechanical factors on the structure of blood vessels and other deformable channels. Thus, it has been shown[1] that flow at critical velocities through a deformable channel can lower the pressure on a localized segment of the wall and induce the development of cushions, valvelike structures, stenoses, and other formations resembling those in the vascular system.

Animal experiments have suggested that the endothelium of the blood vessels is normally compressed by the lateral force of the blood pressure.[2] When the lateral pressure is high, it tends to flatten the endothelium, and, by a process akin to pressure atrophy, prevents it from proliferating. At sites of increased velocity the endothelium appears to be released from the compressive atrophic forces, and intimal proliferation may proceed, with the development of cushions and other structures.

In model experiments it has been noted that cushions and stenoses never develop upstream from a severe narrowing of the lumen.[1] This observation suggested the possibility that a high upstream pressure might prevent the development of a stenotic process. The following experiments were undertaken to analyze these forces which presumably might affect the tendency to vascular closure.

METHODS

A hemicylindrical groove of 6.4 cm. radius was cut in a board of hard transparent plastic, 1 cm. thick (Fig. 1). Transparent deformable silicone rubber† was pressed into this groove. A half-round channel was then molded in the silicone by means of a template consisting of a dowel mounted on a jig. Care was taken to remove excess silicone and to avoid irregularities in the shape of the channel. A tapered inlet, 2 cm. long, reduced the tendency to disturbances of the stream at the inlet, helping to maintain laminar flow. A second board was prepared in a similar manner. The two boards were then apposed so that a continuous tube of silicone was formed, enclosed in the grooves in the boards (Fig. 2). In the present study the diameter of the lumen was about 6.4 mm., and the thickness of the silicone wall was about 3.2 mm.

From the University of Buffalo Chronic Disease Research Institute, Buffalo, N. Y. (The Institute is supported in part by the New York State Department of Health.)

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†Obtained from Silicone Products Department, General Electric Company, Waterford, N. Y., Catalog SE-30, water white, specific gravity 0.98.

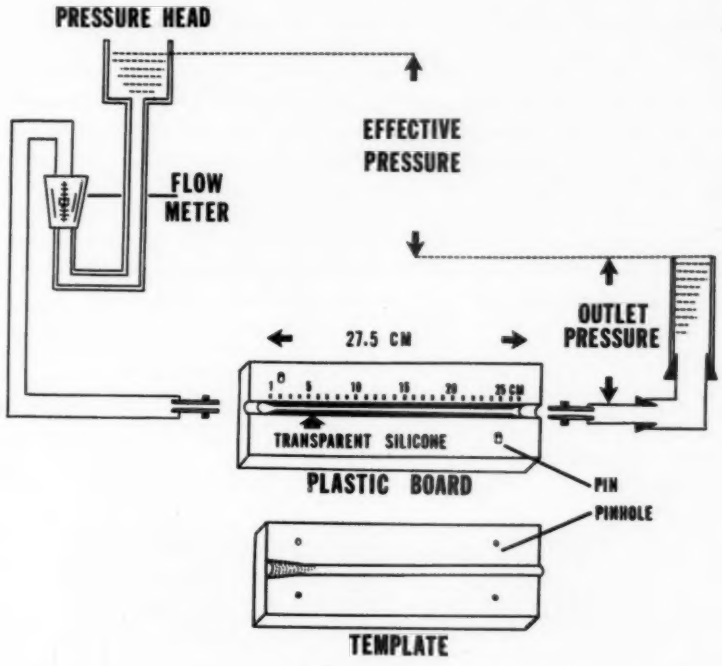

Fig. 1.—The arrangement used in the present study. Water flowing from a pressure head through a flowmeter entered the channel of transparent silicone which had been formed by use of the template. An outlet pressure was supplied by an overflow column. The effective pressure equaled the difference between the pressure head and the outlet pressure.

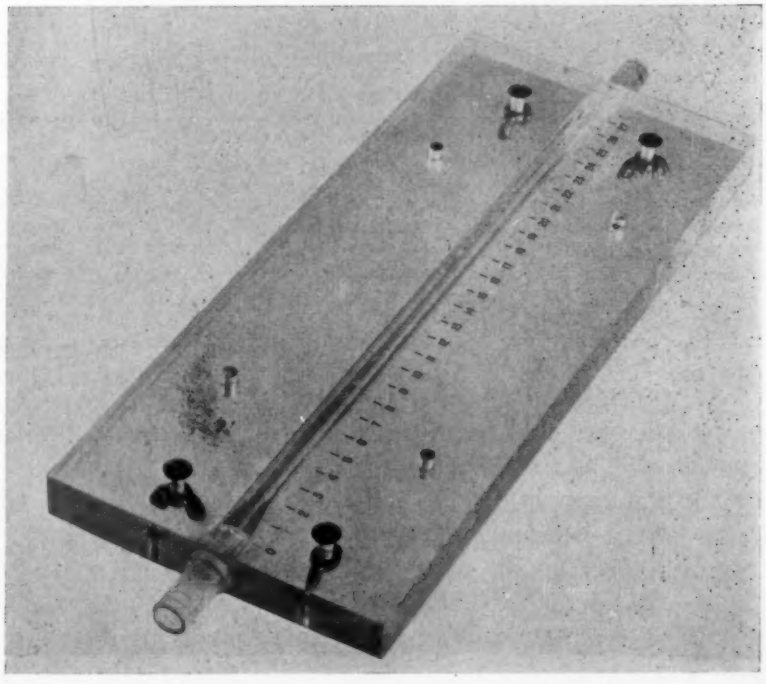

Fig. 2.—Assembled model. Flow enters from the source at the left and leaves at the right. The silicone lining the channel may be seen as the relatively light layer. Distance is marked in centimeters.

A source of constant pressure was maintained in a water reservoir at a fixed height, with an overflow tube arranged to prevent the pressure from rising above the predetermined value. The water passed from the reservoir via a wide rubber tube to a direct-reading rotameter and entered a straight horizontal tube, 1 meter long. In this manner, flow irregularities were reduced and a laminar flow pattern was established before the water entered the inlet of the silicone tube. At the outlet of this tube the water was delivered directly into a sink, or into a wide vertical pipe arranged so that overflow would occur at a fixed height (Fig. 1). In this way it was possible to study the effects of selected (1) effective pressure heads and (2) flow rates at (3) various outlet pressures. The rate of flow was recorded at regular intervals, and the time of closure of the tube was noted. The addition of vegetable dye to the water perfusing the tube aided in the observation of the changes in the channel.

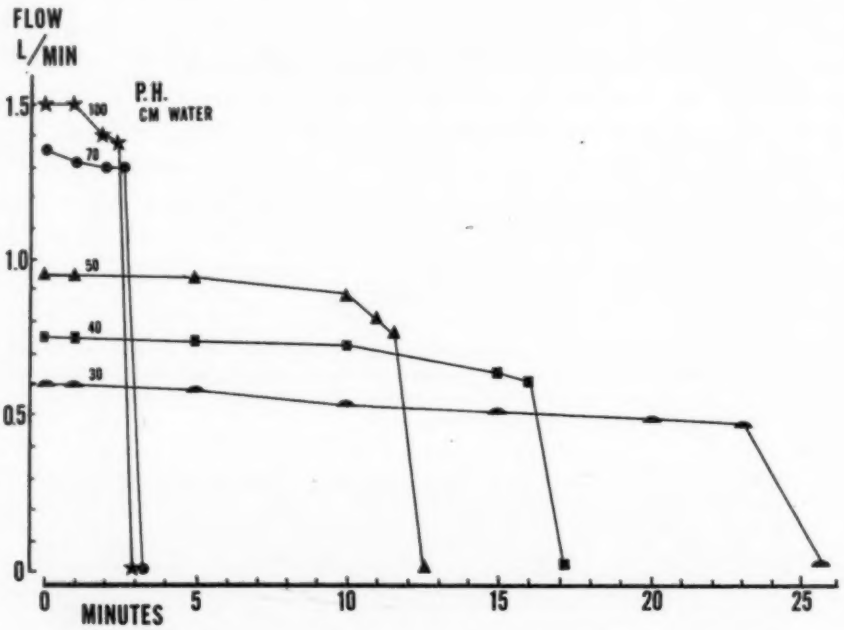

Fig. 3.—Effect of pressure head and volume of flow on time of closure. Flow is given in the ordinate in liters per minute. The abscissa is given in minutes from the onset of flow. The pressure heads (*P.H.*) are noted near the beginning of each line as 30, 40, 50, 70, or 100 cm. water. Each dot represents the average of at least 4 trials. Discussed in text.

RESULTS

A total of 68 experiments was carried out.

1. *Stasis.*—The outlet was obstructed and the system was filled with water at pressure heads ranging from 30 to 100 cm. of water with no flow. No changes were observed in the channel over the course of 24 hours in any of these experiments. These static experiments demonstrated that pressure alone, applied uniformly, had no effect on the deformable material. These results are due to the fact that the specific gravity of the silicone is nearly equal to that of water, reducing the likelihood that some of the changes might be due to difference in density.

2. *Flow and Closure.*—With pressure heads of 30 cm. of water and initial rates of flow as low as 0.6 liter per minute, the delivery remained unchanged for

a minute or so (Fig. 3). Flow then declined slowly over the next 20 minutes, and the delivery at the end of this period was 0.45 liter per minute. At this point the flow fell sharply, in association with the development of a localized constriction which was easily visualized because of the transparent nature of the wall. The initial closure often occurred at a site a few centimeters beyond the inlet. Direct examination revealed that a conelike stenosis had developed (Fig. 4). A small jet through the remaining tiny orifice was evident.

After its formation, the narrowing migrated slowly downstream at a rate which depended on the effective pressure head. The tube upstream from the stenosis gradually widened, probably as a result of the higher pressure in this part of the tube.

When the migrating stenosis reached the outlet, a small amount of silicone was extruded from the end of the tube, following which the flow was again resumed, but at a rate somewhat less than that obtaining at the onset of the experiment.

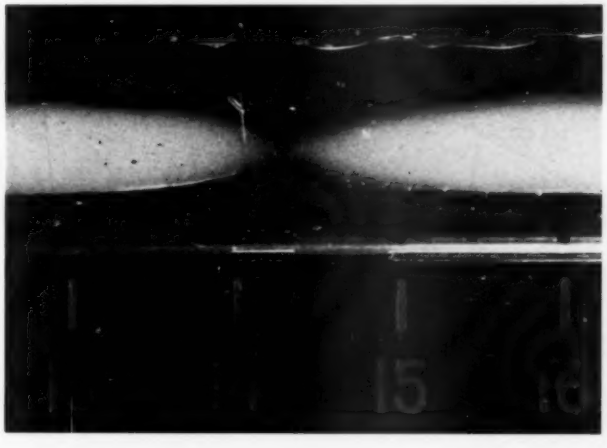

Fig. 4.—Characteristic stenosis of silicone tube. This occurred after 25 minutes of flow, using a pressure head of 70 cm. water and an outlet pressure of 30 cm. water.

3. *Recurrent Stenosis.*—After a period of time less than that required for the formation of the first occlusion, a second closure occurred. In some models the process was observed during a succession of closures (Fig. 5). In each instance, less time was required for this to occur than for the previous occlusion. The shortened time required for the development of a stenosis was attributed to the persistence of irregularities introduced into the channel by the previous passage of the stenosis. Increased velocities and rotational nonlaminar flow could be seen at these irregular, partially narrowed sites, and these forces probably contributed to earlier closure.

4. *Effective Pressure Head.*—In previous studies on a deformable tube with a rectangular cross section the time required for closure was related to the pressure head utilized, and to the volume of flow. Similar data were obtained with pipes of circular cross section used in the present series. Fig. 3 shows that the closure is accelerated at higher effective pressures and flow rates. In general,

the rate of closure could be related to the square of the initial flow velocity. Stenosis was seen as early as 3 minutes after the onset of flow at pressure heads of 100 cm. of water, while heads of 30 cm. required about 25 minutes. Intermediate pressures produced closures at intermediate times. In other studies, using higher pressure heads and flows, closures could be produced repeatedly in as little as 10 seconds.

5. *Inhibitory Effect of Outlet Pressure.*—Outlet pressure was applied to the system by causing the effluent to enter an overflow system consisting of a wide vertical tube of selected height (Fig. 1). The closure of the deformable channel was delayed progressively as the outlet pressure was increased (Fig. 6). The time prior to closure was doubled as the outlet pressure was increased from zero to approximately 30 cm. of water. The second and third stenoses developing in a prepared silicone tube were delayed in a similar manner by outlet pressure (Fig. 5).

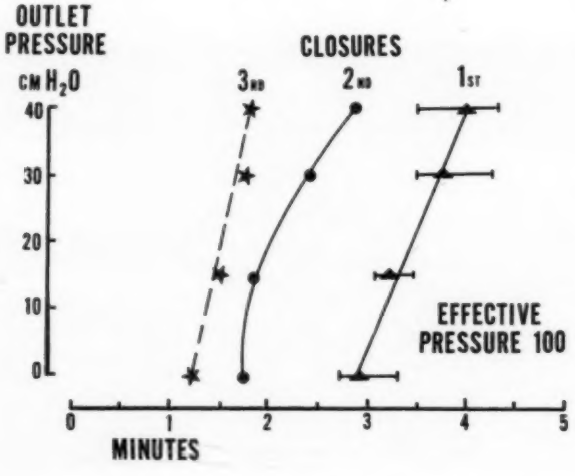

Fig. 5.—Time for closure. At an outlet pressure of zero, the first closure occurred at 3 to 4 minutes; the second closure occurred in 1¾ minutes after flow was resumed, and the third closure in 1¼ minutes. The effects of heightened outlet pressures on time of closure are also shown. Discussed in text.

DISCUSSION

The results are discussed first from the point of view of the physical forces producing changes in a deformable channel; these forces are then analyzed in terms of how they might affect the structure of blood vessels.

Mechanical Factors.—In our models the time required for the production of a narrowing is determined by the effective pressure head and the rate of flow, with closure occurring more quickly at higher velocities. The tendency to closure is probably initiated as a result of the occurrence of an increased velocity at a given level in the tube, reducing the distending pressure at this site. The higher pressure at adjacent regions extrudes silicone into the regions of lower pressure, causing a local accumulation and narrowing of the channel. At the narrowing the velocity of the stream increases further, the lateral pressure falls still more, and the process of closure becomes progressive.

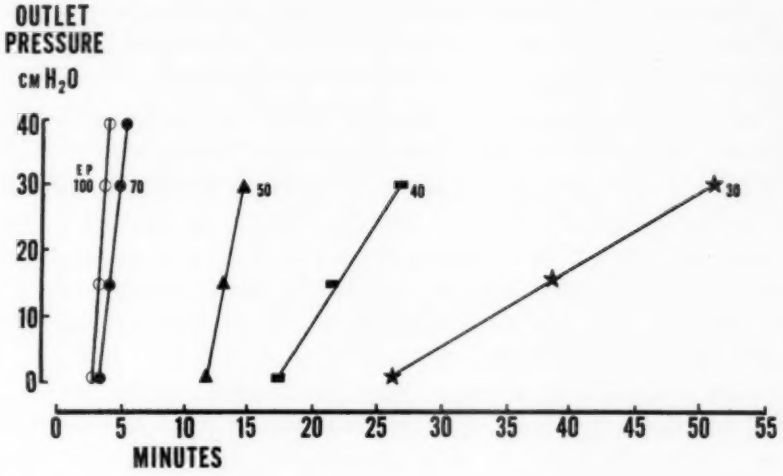

Fig. 6.—Time of closure of silicone tube on horizontal axis related to outlet pressure on vertical axis. Effective pressure (*EP*) head (inlet pressure minus outlet pressure) is given adjacent to each line. Time of closures at outlet pressures of 0, 15, 30, and 40 cm. water are shown for effective pressure heads of 30, 40, 50, 70, and 100 cm. water. Each dot represents the average of at least 4 trials. The delay in closure as outlet pressure is elevated may be seen. Discussed in text.

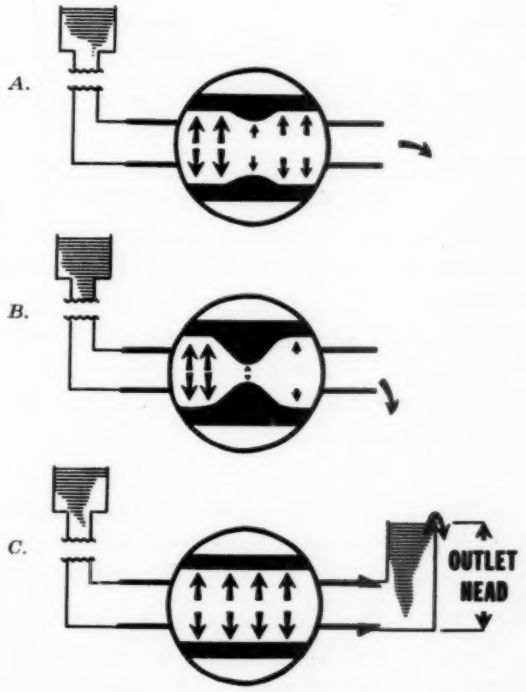

Fig. 7.—A suggestion on the mechanics of inhibition of stenosis by outlet pressure. The reservoir providing the pressure head is shown at the left. In *A*, the portion of the channel in the circle is "magnified," with large arrows showing the high pressure compressing the silicone (black line) upstream, small arrows at the narrowing representing the region of high velocity and reduced pressure, and intermediate-sized arrows beyond the narrowing. In *B*, the stenosis is more severe; the upstream pressure is greater, the pressure at the narrowing is very small, permitting encroachment of the lumen, and the pressure downstream is low. In *C*, the presence of an outlet head increases the pressure fairly uniformly throughout the system and inhibits the development of sites of high velocity and low pressure.

After migration of the stenosis to the outlet and the resumption of rapid flow the region of the tube which had remained partially narrowed, and in which the velocity of the stream was greatest, became the site of the succeeding stenosis.

The delay in the development of stenosis when outlet pressures were applied appeared to be determined by the resulting general increase in lateral pressure in the tube (Fig. 7). This increased distending pressure reduces the tendency of the silicone to move into the lumen, thereby inhibiting closure. Previous experiments have also shown that closures do not ordinarily occur on the upstream side of a stenosis, apparently because of the elevated lateral pressure in that segment of the tube. If the vessel containing the silicone were distensible, the increased pressure would also tend to widen the lumen and thereby reduce the velocity and the tendency to upstream closure. These results have a similarity to those of previous studies on collapsible tubes, wherein it was shown that outlet pressures may inhibit flutter of the walls and actually result in an increased flow.[3,4]

Biological Considerations.—A rise in lateral pressure in a blood vessel tends to compress and flatten the lining cells and presumably thereby to inhibit the proliferative tendencies of this cellular layer.[5] An increase in the velocity of the stream may be expected to reduce the compression acting on the endothelium at this site. Whenever this effect is marked, the endothelial cells can round up and proliferate, and intimal cushions may be produced. Such sites of increased velocity tend to occur at convergences, as in veins and lymphatic vessels, and at "sinks," as are present at the atrioventricular junction when the low pressure in the relaxing ventricle permits rapid inflow during diastole.

Cushion development of sufficient degree to produce obstruction to flow has been observed in earlier models which had squared channels.[1] However, in the cylindrical models used in the present study the stenoses have been cone-shaped (Fig. 4). These cones are grossly similar in form to the stenoses of the pulmonary valve and of coarctation. After formation the stenotic process persists, since the high velocity of the stream through the orifice drops the local pressure to a point at which local intimal proliferation may continue. Stenoses thus may tend to persist and to grow more severe, despite the high pressures in the upstream segment and the great force which beats intermittently against the occluding diaphragm.

It is suggested that the high lateral pressure prevailing in the arterial tree maintains the normal endothelium in a flattened, nonproliferative phase, and thereby acts against the development of cushions, valves, and stenoses.

While valves do not ordinarily occur in arteries, cushions and stenoses are sometimes seen. Cushions may result from local trauma or injury or may follow lipid or other infiltrations of the vessel wall. The development of an atheroma provides a site for streamline deviation, local lowering of pressure, and may release the proliferative potential of the vessel lining. A progressive stenotic process may thus result. Having formed, the constrictive process persists, since the velocity is high in the region of the narrowing and the proliferative process will tend to go to complete stenosis. The development of a narrowing in an artery tends to lower its own outlet pressure, and thereby accelerates the process.

The results permit the suggestion that the presence of collaterals adequate to maintain a high outlet pressure may delay or even inhibit the stenotic process. The present results with deformable silicone also suggest the possibility that a stenosis may migrate downstream from its original site, as long as the channel remains deformable. It is possible that such migration may occur in the embryonic heart or blood vessels.

SUMMARY

Flow at critical velocities through a deformable tube lined with silicone results in the development of a "coarctation" with a tiny orifice remaining.

An increase in the pressure at the tube outlet inhibits the tendency for closure, probably by raising the lateral pressure in the upstream portions of the system. The results suggest that a high lateral pressure such as that ordinarily present in arteries may operate to inhibit cushion formation, valvulogenesis, and stenosis. The implications of these findings in the production or inhibition of the stenotic process are discussed.

The plastic boards and templates were prepared by Mr. Arthur Baase of the Institute Machine Shop. Technical assistance was given by Richard Lyman, Jr.

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A Vectorcardiographic Analysis of Left Ventricular Strain Pattern Comparatively Studied With ST-T Change of Left Bundle Branch Block and Ventricular Premature Beat of Right Ventricular Origin

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INTRODUCTION

Besides Schellong's work, there has been a considerable number of studies made on the vectorcardiogram. These studies have been directed mostly toward a ventricular depolarization process, and have resulted in a creditable interpretation of ventricular hypertrophy, bundle branch block, posterior myocardial infarction, etc.

It is understood that ST-T changes have the most important clinical significance of all ECG findings. At present, however, except for the coronary T, which is rather characteristic and easy to differentiate, ST-T changes are difficult to analyze in evaluating the kind and severity of abnormalities. Thus, ST-T changes are generally called myocardial changes or myocardial damages.

Now, it seems very interesting to make a vectorcardiographic study of ST-T changes which have not yet been adequately analyzed. This kind of approach, which has some technical difficulties, has been tried by few researchers except Kimura,[1-8] Portheine,[9] Karini,[10-12] etc. Of all the ST-T changes that are usually encountered, the most common is the left ventricular strain pattern (used in the present instance to denote the mere form of curve, signifying inverted T and slight ST depression with upward convexity in left precordial leads and/or Lead V_L (aV_L), i.e., what is called in another interpretation the ST-T change of left ventricular hypertrophy). An attempt is here being made to analyze this pattern vectorcardiographically.

First, the orientation and the configuration of the T loop of the left ventricular strain pattern are observed and classified. The results obtained are reviewed in reference to clinical findings. Thus, the T-loop changes are arranged in a serial grading of severity. Furthermore, from the standpoint of ventricular gradient the significance of T-loop changes is discussed together with the interpretation of the T loop of left bundle branch block and ventricular premature beat of right ventricular origin.

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MATERIALS AND METHODS

Selected for study were 148 patients who showed a left ventricular strain pattern or a transitional pattern between the normal pattern and the left ventricular strain pattern, i.e., the pattern with trend of flat and (− +) biphasic T in left precordial leads and/or Lead V_L (aV_L), etc. All of the patients demonstrated hypertension or aortic valvular disease and/or, roentgenologically, left ventricular enlargement.

The 8 patients with left bundle branch block who were studied for comparison were clinically diagnosed as follows: 7 with coronary heart disease and 1 with combined (aortic and mitral) valvular disease. One of the 7 patients with coronary heart disease showed a high lateral myocardial infarction of recent stage in his previous electrocardiogram.

Ventricular premature beat was also studied in 14 patients. It was of right ventricular origin, since the form of its QRS complex was similar to that of left bundle branch block. Ten of the 14 patients showing ventricular premature beat were free from any clinical signs of heart disease. One of these 10 patients had suffered from diabetes mellitus. In the other 4 patients the findings were of myocardial changes in the QRS-T complexes in basic rhythm; 3 of these patients were diagnosed as having coronary heart disease, and 1, on autopsy, showed left ventricular hypertrophy of unknown etiology.

The Technicon cardiograph was used; and the Grishman cube system[13] was adopted.

Observations were made of a whole figure of the QRS loop and the T loop, as well as of the vicinity of the origin and the T loop enlarged at increased amplification. Three plane photographs were taken simultaneously with 35-mm. films.

In surveying the clinical aspect, cardiac incompetence was determined on clinical findings. Also included was obvious angina on effort. The standard used for the foregoing determination corresponded to second degree and above in the classification of the New York Heart Association.

Seventy-one of the 148 patients had undergone roentgenography of the heart (target distance 2 M.). Then, maximum transverse diameter (Tr), median-left diameter (M_1), long diameter (L), etc., were measured on the posteroanterior view.

QRS-T complexes of Leads I and II were projected on paper and enlarged with a projector. The projected area was measured by a planimeter for calculation of the ventricular gradient.

The orientation of three plane projections of VCG in the present study is shown in Fig. 1.

RESULTS

T LOOP OF LEFT VENTRICULAR STRAIN PATTERN

1. *Classification.*—The T loop of the left ventricular strain pattern is divided roughly into five types on the basis of orientation and configuration (Table I):

TABLE I. NUMBER OF CASES CLASSIFIED BY TYPE (GRADE) OF T LOOP IN REFERENCE TO SPATIAL ORIENTATION OF T LOOP

TYPE OF T LOOP	TOTAL NUMBER OF CASES	ORIENTATION											
		L:P.I.	L.I.	L.A.I.	A.I.	I.	R.A.I.	R.A.	R.A.S.	R.I.	R.	R.S.	R.P.S.
I	31	1	2	18	7	3	0	0	0	0	0	0	0
II	28	0	0	0	0	0	23	2	2	0	0	0	1
III	34	0	0	0	0	0	22	0	11	0	1	0	0
IV	18	0	0	0	0	0	12	2	3	0	1	0	0
V	37	0	0	0	0	0	1	1	35	0	0	0	0

L: left; R: right; A: anterior; P: posterior; S: superior; I: inferior.

Type I (31 cases) (Fig. 2): The T loop is situated mostly to the left, anteriorly and inferiorly, protruding from the QRS loop and stituated right and anteriorly to the QRS loop. The direction of the long axis of the T loop is to the left in most cases, inferior and slightly anterior; the direction of inscription of the T loop is counterclockwise in horizontal view, clockwise in right sagittal view, and counterclockwise in frontal view. But in the right sagittal view some cases demonstrate the centrifugal and centripetal limbs of the T loop almost superposed. Such a trend is also found in the other four types.

Type II (28 cases) (Fig. 3): The T loop is completely protruded from the QRS loop; it is situated mostly to the right and anteroinferiorly, and in some cases to the right and anterosuperiorly, and sits almost opposite to the QRS loop. The direction of inscription is the same as that of Type I. As described below, in most of the cases belonging to this type the QRS loops are open. In such cases the terminal portion of the QRS loop proceeds smoothly to connection with the centrifugal limb of the T loop; they seldom show a conspicuous angle in this junction.

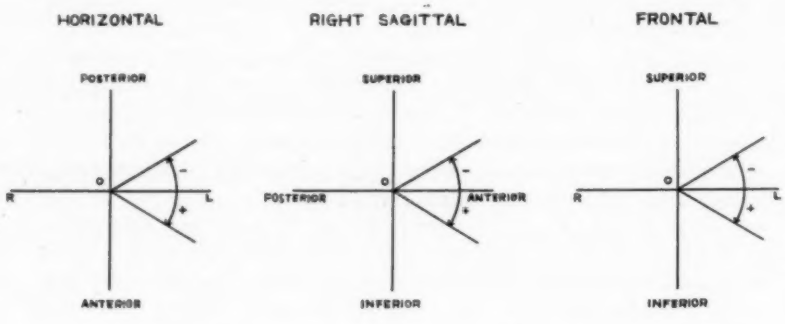


Fig. 1.—Orientation and sign of angle in three plane projections of VCG in the present study.

Type III (34 cases) (Fig. 4): As in Type II, the T loop is situated to the right and anteroinferiorly, and in some cases to the right and anterosuperiorly. But the centrifugal limb of the T loop is situated more anteriorly than the centripetal limb; it or the terminal portion of the QRS loop is crossed with the centripetal limb of the T loop in horizontal view. Hence, the direction of inscription of the T loop is clockwise in horizontal view. But it is the same as in Types I and II in two other views, i.e., clockwise in the right sagittal view and counterclockwise in the frontal view.

When the terminal portion of the QRS loop is crossed with the centripetal limb of the T loop, and the J point (corresponding to the RS-T junction in the ECG) is situated more anteriorly to the centripetal limb of the T loop, the loop very often makes a nearly right angle at the J point.

Type IV (18 cases) (Fig. 5): The T loop is situated in most cases to the right and anteroinferiorly, and in some cases to the right and anterosuperiorly. The direction of inscription of the T loop is the same as that of Type III in horizontal view and right sagittal view. The terminal portion of the QRS loop or the centrifugal limb of the T loop is crossed with the centripetal limb of the T loop,

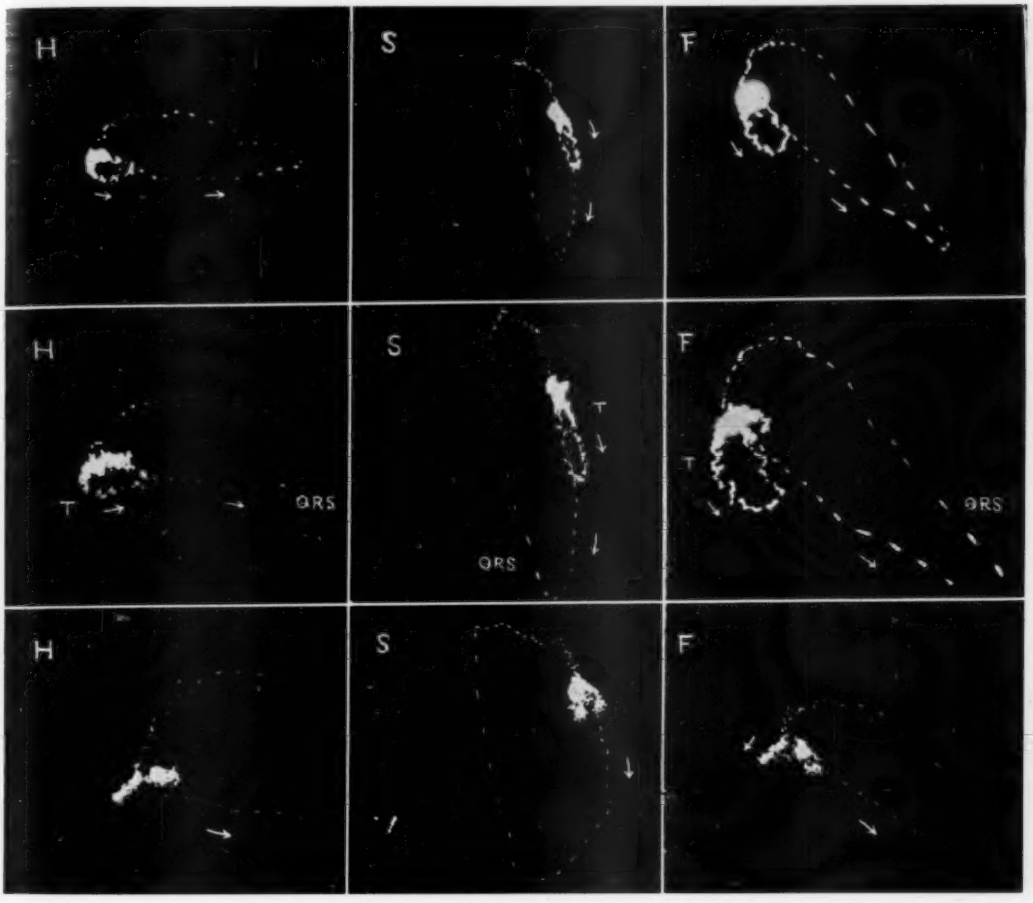


Fig. 2.—Patient S.W., a 50-year-old man with hypertension. *A*, Whole figure of QRS loop and T loop; T-loop change is of Type I (Grade I). *B*, The vicinity of the origin and the T loop recorded at higher amplification. *C*, VCG recorded before treatment; T loop shows change of higher grade. (The arrows indicate the direction of inscription.)

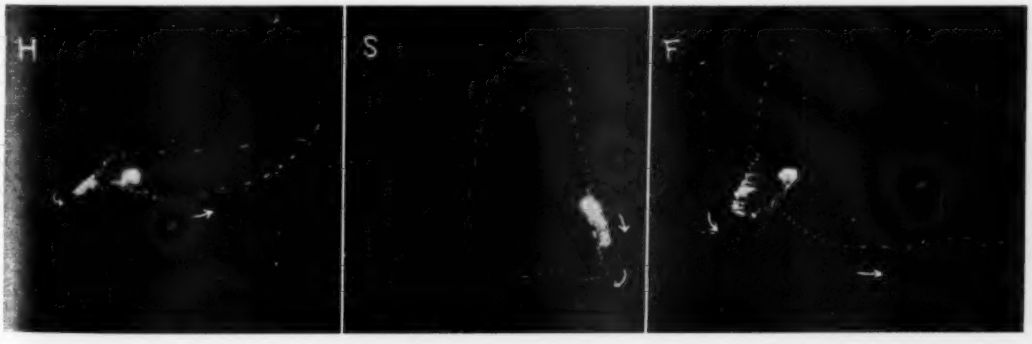


Fig. 3.—Patient N. Y., a 39-year-old man with aortic regurgitation. The vicinity of the origin and the T loop recorded at increased amplification. T-loop change is of Type II (Grade II).

not only in the horizontal view but also in the frontal view; the J point is situated anteroinferiorly to the centripetal limb of the T loop. Accordingly, the direction of inscription of the T loop is clockwise in the horizontal, right sagittal, and frontal views. However, in cases in which the T loop is situated to the right and anterosuperiorly, the direction of inscription of the T loop is clockwise in horizontal view, counterclockwise in right sagittal view, and counterclockwise in frontal view.

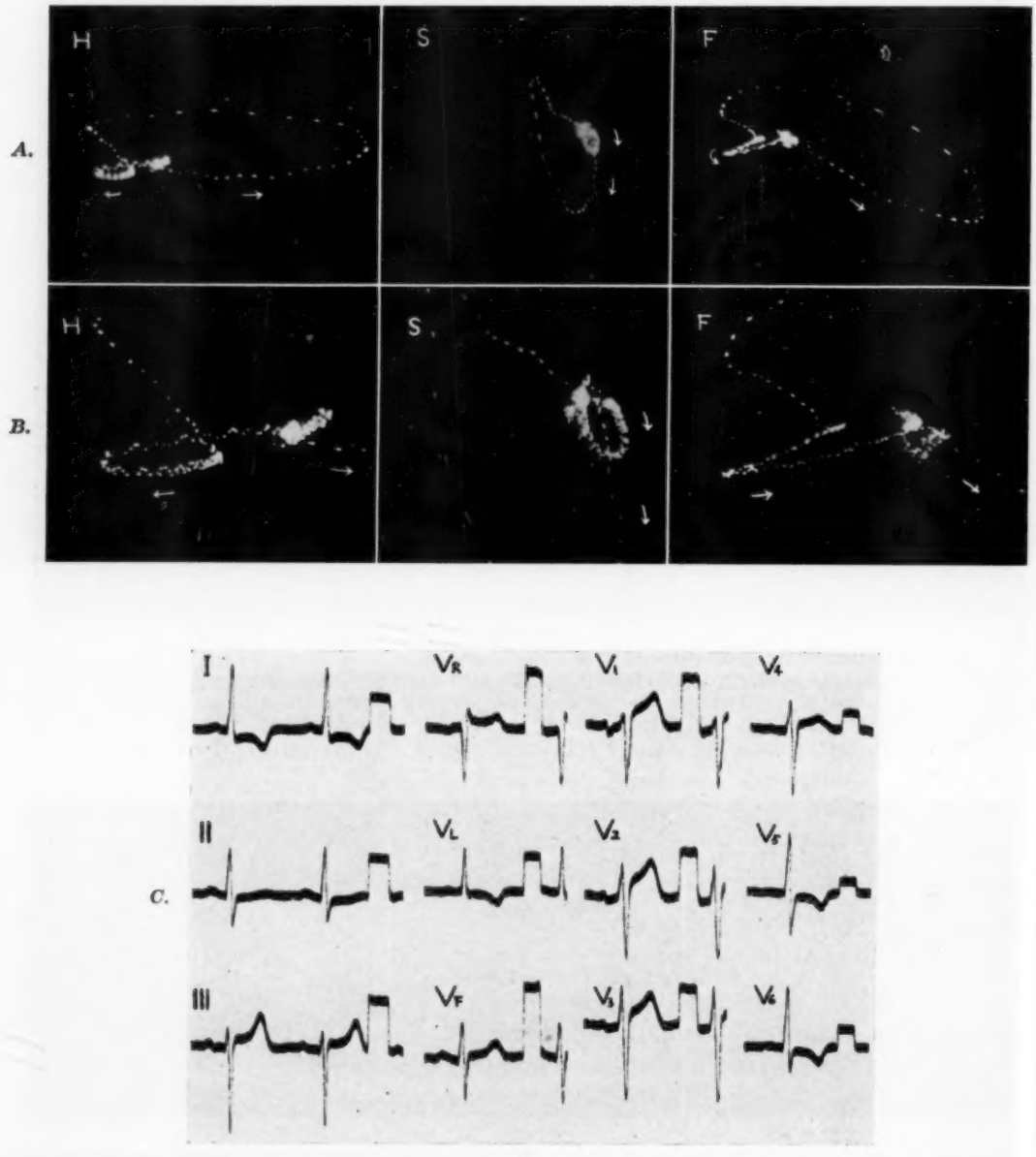


Fig. 4.—Patient G. Y., a 50-year-old man with hypertension. *A*, Whole figure of QRS loop and T loop. T-loop change is of Type III (Grade III). *B*, The vicinity of the origin and the T loop recorded at increased amplification. *C*, Electrocardiogram recorded on the same patient.

Type V (37 cases) (Fig. 6): The T loop is situated, generally, to the right and anterosuperiorly. The direction of inscription is the same as that of Type IV in horizontal and frontal views. But the J point is situated anteroinferiorly to the centripetal limb of the T loop, not only in horizontal and frontal views but also in right sagittal view. Accordingly, the direction of inscription of the T loop even changes to counterclockwise in right sagittal view, i.e., it is clockwise in horizontal view, counterclockwise in right sagittal view, and clockwise in frontal view.

The spatial orientation of the T loop of each type is described in detail in Table I.

2. *J Vector.*—As is obvious from the foregoing description, the QRS loop becomes open in accordance with the changes in the T loop, resulting in the development of the J vector (ST vector), which corresponds to the RS-T junction in the ECG. In vectorcardiography the S-T segment and T wave of the ECG are combined together to make the T loop.

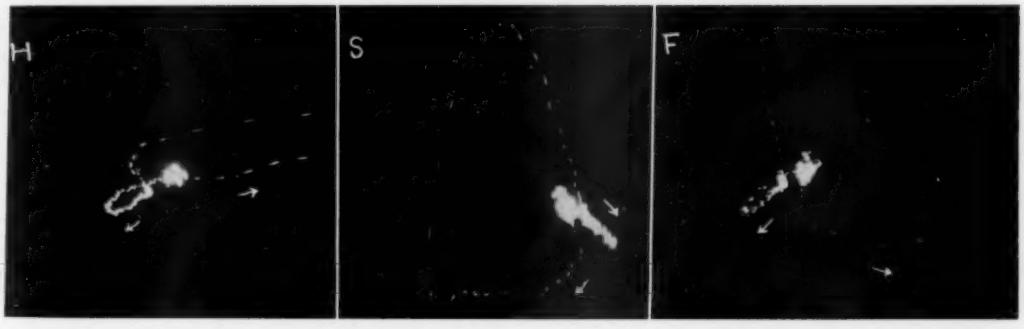


Fig. 5.—Patient S. W., a 70-year-old man with hypertension. The vicinity of the origin and the T loop recorded at higher amplification. T-loop change is of Type IV (Grade IV).

In Type I, about half of the cases clearly showed a J vector. In Types II, III, IV, and V, except for relatively few cases, the J vector generally was observed. The direction of the J vector was mostly right-anterior-inferior, right-anterior, or right-anterior-superior for Type I, right-anterior, right-anterior-superior for Types II and III, right-anterior for Type IV, right-anterior-superior for Type V. Except for Type I, the direction of the J vector was nearly parallel with the long axis of the T loop.

The direction of the J vector is described in detail in Table II.

3. *QRS Loop, Followed by Left Ventricular Strain Pattern.*—The QRS loop in the case of overloading of the left ventricle is described by Grishman[13,14]; i.e., the QRS loop is situated mostly to the left and inferiorly, showing a slight backward deviation; the QRS loop indicates in most cases a counterclockwise inscription in horizontal view, and in some cases a figure-of-eight with its clockwise distal portion; the QRS loop shows a clockwise inscription in right sagittal view; it shows in most cases a counterclockwise inscription in frontal view, and in some cases a clockwise inscription.

The present study considered the relationship between the type of T loop and the direction of the long axis of the QRS loop in horizontal view. On an average, the direction of the long axis of the QRS loop was $-6.3° \pm 1.33°$ for Type I; $-11.0° \pm 1.98°$ for Type II; $-13.1° \pm 1.83°$ for Type III; $-8.2° \pm 1.70°$ for Type IV; and $-12.0° \pm 1.35°$ for Type V (Fig. 7). Some differences among the types of T loop were found, but these did not seem statistically significant.

A counterclockwise inscription of the QRS loop in the horizontal view was demonstrated in 30 of 31 cases of Type I, 25 of 28 cases of Type II, all cases of Type III, 17 of 18 cases of Type IV, and 31 of 37 cases of Type V. The other

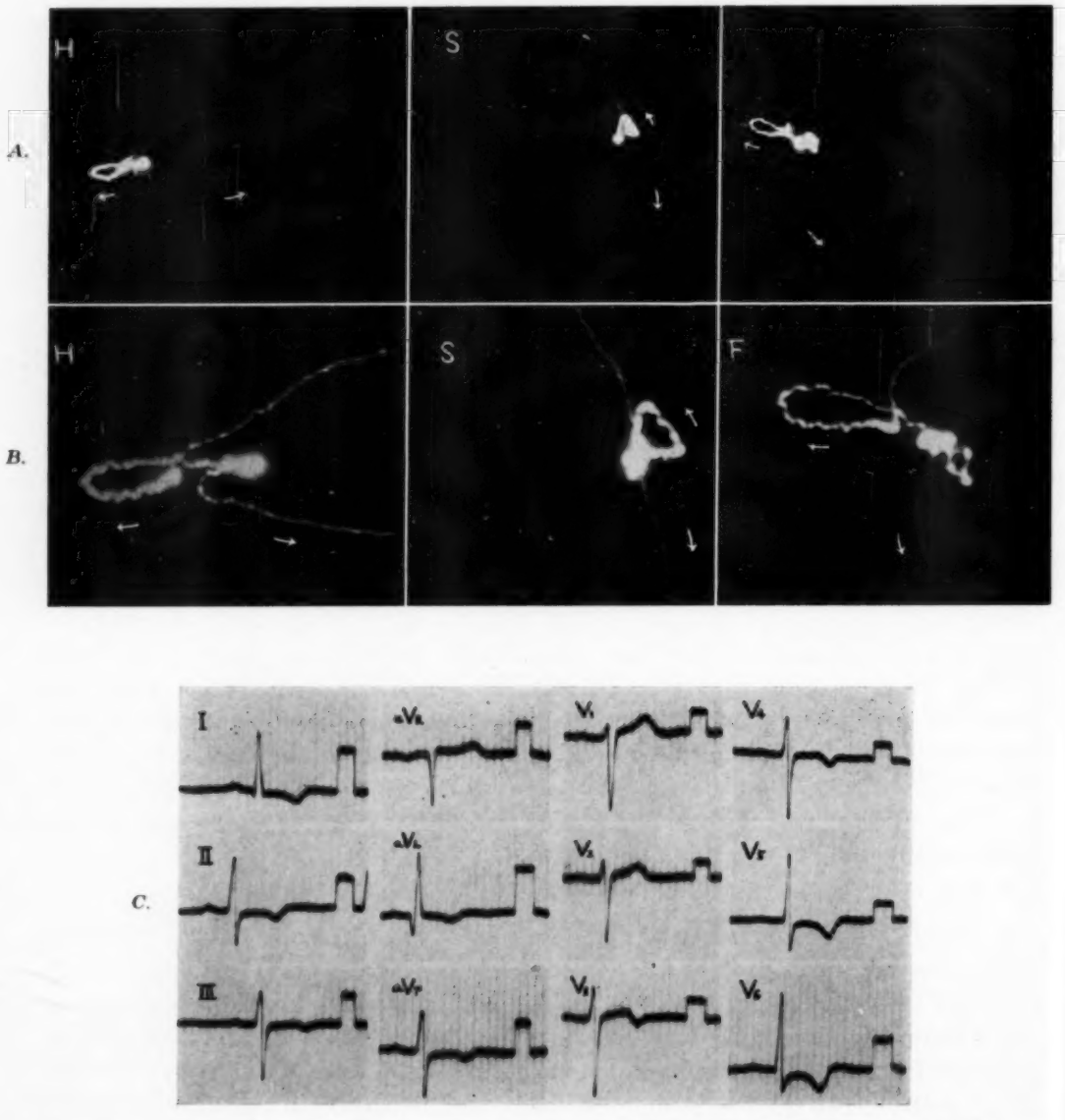


Fig. 6.—Patient K. K., a 54-year-old man with hypertension. *A*, Whole figure of QRS loop and T loop. T-loop change is of Type V (Grade V). *B*, At increased amplification. *C*, Electrocardiogram.

cases showed a figure-of-eight with its clockwise distal portion. Those with the figure-of-eight inscription proved to be cases of aortic regurgitation. Discussions of the figure-of-eight have been made in other papers.[15,16]

The direction of inscription of the QRS loop in the right sagittal view was clockwise for all cases.

The direction of inscription of the QRS loop in frontal view was found to be counterclockwise in 23 cases of Type I, 24 cases of Type II, 30 cases of Type III, 15 cases of Type IV, and 29 cases of Type V; the others were clockwise or figure-of-eight (Table III).

4. *Clinical Aspect.*—A roentgenologic examination was performed on the hearts of 71 patients, and the relationship between the feature of the T loop and the extent of cardiac enlargement was studied.

The maximum transverse diameter (Tr) of the heart tended to increase with progression from Type I through Type V (Fig. 8). In Fig. 8 the white circles indicate cases of aortic regurgitation, and the black circles indicate cases of hypertension and others. Generally, in this figure the Tr seems to be larger in cases of aortic regurgitation than in cases of hypertension and others. Three

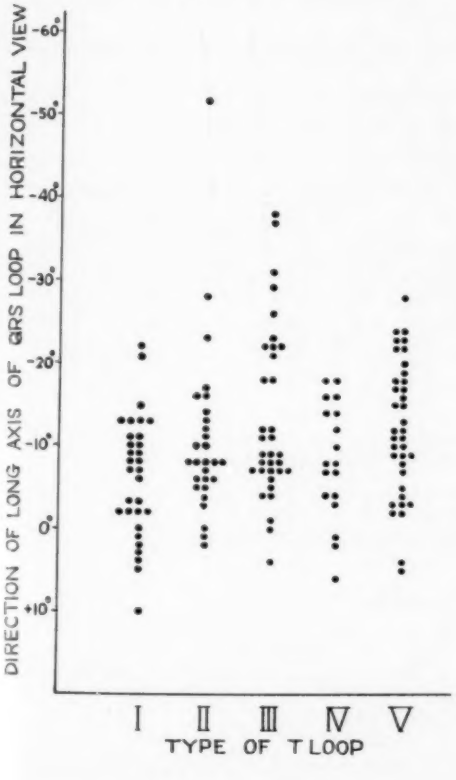


Fig. 7.

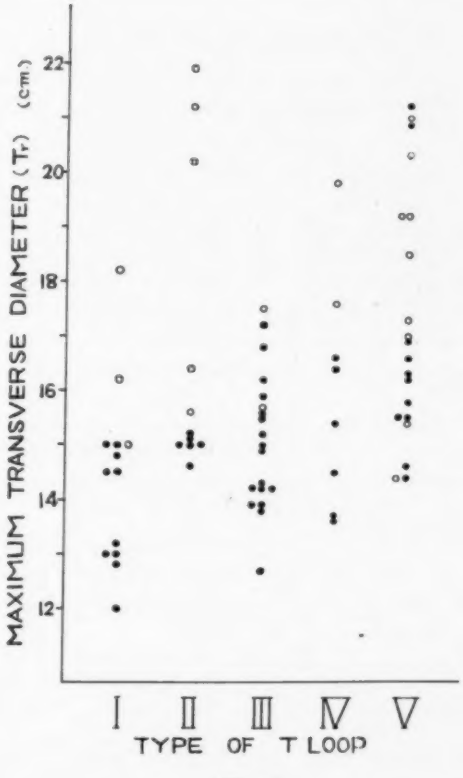


Fig. 8.

Fig. 7.—Direction of the long axis of the QRS loop in horizontal view in cases of each type of T-loop change.

Fig. 8.—Transverse diameter in cases of each type of T-loop change. The white circles indicate cases of aortic regurgitation. The black circles indicate cases of hypertension and others.

instances of exceptionally large Tr in cases of Type II are those of aortic regurgitation. These patients were in congestive heart failure; findings in regard to them will be interpreted and discussed later.

Likewise, the cases of larger median-left diameter (M_l) increased in accordance with progression from Type I through Type V, and the same was true also for cases of long diameter (L). In regard to cardiac measurement it is generally understood throughout that with the progression from Type I through Type V the cases of large value increase, although cases of small value are also found.

Next, the incidence of cardiac incompetence was studied in cases showing the various types of T loop (Table IV). Among those with Type-I T loop there was 1 case of angina on effort; among those with Type II there were 3 cases of congestive heart failure; among those with Type III there were 3 cases of angina on effort and 6 cases of congestive heart failure; among those with Type IV there was 1 case of angina on effort and 3 cases of congestive heart failure; and among those with Type V there was 1 case of angina on effort and 13 cases of congestive heart failure. Types II-V, which show the QRS and T loops to be discordant, result in the development of cardiac incompetence, there being an especially

TABLE II. NUMBER OF CASES CLASSIFIED BY TYPE (GRADE) OF T LOOP IN REFERENCE TO SPATIAL DIRECTION OF J VECTOR

TYPE OF T LOOP	TOTAL NUMBER OF CASES	DIRECTION							
		R.A.I.	R.A.	R.A.S.	R.I.	R.	R.S.	R.P.S.	OBSCURE
I	31	5	5	6	0	1	0	0	14
II	28	1	5	10	1	3	3	1	4
III	34	2	3	25	0	2	0	0	2
IV	18	0	12	2	3	0	1	0	0
V	37	4	3	24	0	1	1	1	3

R: right; A: anterior; I: inferior; S: superior; P: posterior.

TABLE III. NUMBER OF CASES CLASSIFIED BY TYPE (GRADE) OF T LOOP IN REFERENCE TO DIRECTION OF INSCRIPTION OF QRS LOOP IN FRONTAL VIEW

TYPE OF T LOOP	TOTAL NUMBER OF CASES	DIRECTION OF INSCRIPTION OF QRS LOOP				
		COUNTER-CLOCKWISE	FIGURE-OF-EIGHT		DOUBLE CROSSED	CLOCKWISE
			WITH COUNTERCLOCKWISE DISTAL PORTION	WITH CLOCKWISE DISTAL PORTION		
I	31	23	1	2	0	5
II	28	24	2	0	0	2
III	34	30	0	2	0	2
IV	18	15	1	0	1	1
V	37	29	2	4	0	2

high incidence in Type V, while Type I, which corresponds to slight T-loop change, is excepted. Statistically, as a whole, there exists a relationship between the types of T loop and the incidence of cardiac incompetence (according to χ^2-test, $P < 0.01$).

5. *T Loop and Ventricular Gradient.*—The ventricular gradient in cases with T loop of each type was studied. Since what constitutes a normal range for the ventricular gradient has not been clarified, the values determined by Ashman's measurement[17] were adopted as a normal range in the present study, i.e., male: 8 to 101.2 μV sec., −15° to +95°; female: 1.2 to 89.2 μV sec., −19° to +89°. But the present author in another study[18] revealed that many of the 100 healthy 20- to 30-year-old human beings examined showed a ventricular gradient larger than Ashman's values. However, in the study reported here Ashman's data were adopted, since the group in which the author's measurement was carried out was limited to the age range of 20 to 30 years.

Those cases with T loop of Type I included 2 with abnormally large ventricular gradient and 4 with abnormally directed ventricular gradient; no cases showed overlapping of abnormalities in direction and length (Table V). In the other types all the cases with abnormal ventricular gradient showed only abnormal

TABLE IV. RELATIONSHIP BETWEEN TYPE OF T LOOP AND INCIDENCE OF CARDIAC INCOMPETENCE

TYPE OF T LOOP	TOTAL NUMBER OF CASES	INCIDENCE OF CARDIAC INCOMPETENCE		
		ANGINA ON EFFORT	CONGESTIVE HEART FAILURE (LEFT-SIDED FAILURE ALSO INVOLVED)	TOTAL NUMBER OF CASES WITH CARDIAC INCOMPETENCE
I	31	1	0	1
II	28	0	3	3
III	34	3	6	9
IV	18	1	3	4
V	37	1	13	14

TABLE V. INCIDENCE OF ABNORMAL VENTRICULAR GRADIENT IN EACH TYPE OF T LOOP

TYPE OF T LOOP	TOTAL NUMBER OF CASES	INCIDENCE OF ABNORMAL VENTRICULAR GRADIENT		
		ABNORMAL LENGTH	ABNORMAL DIRECTION	TOTAL NUMBER OF CASES WITH ABNORMAL VENTRICULAR GRADIENT
I	31	2	4	6
II	28	0	3	3
III	34	0	10	10
IV	18	0	6	6
V	37	0	22	22

direction of the ventricular gradient, not abnormal length: among the 28 cases of Type-II T loop there were 3 with abnormal ventricular gradient; among the the 34 cases of Type III, 10; among the 18 cases of Type IV, 6; and among the 37 cases of Type V, 22.

A general trend, excepting Type I, is that the incidence of abnormal cases increases consecutively through the sequence of types. Statistically, as a whole, there exists a relationship between changes in the T loop and abnormalities in the ventricular gradient (according to χ^2-test, $P < 0.01$).

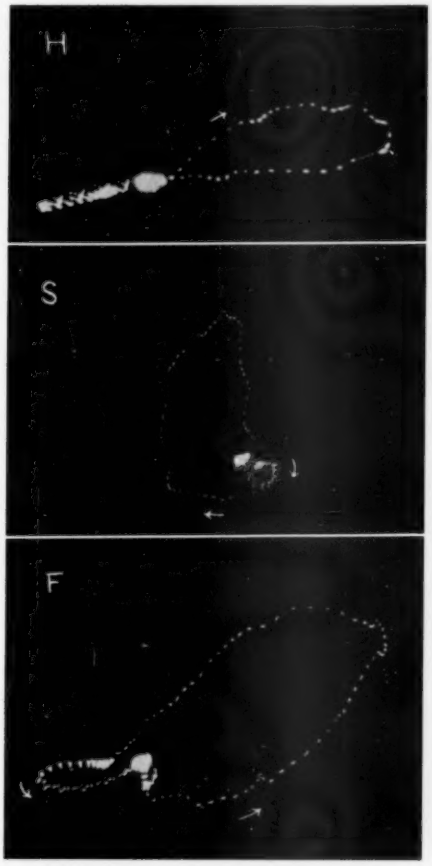
T LOOP IN LEFT BUNDLE BRANCH BLOCK

The clinical diagnosis in 8 patients with left bundle branch block was mentioned above. Two of the 8 patients were in congestive heart failure; in 2 others the presence of congestive heart failure was rather doubtful. Cardiac enlargement was observed in 6 patients. The QRS duration in the ECG was 0.13 sec. for 1 case, 0.14 sec. for 2 cases, 0.15 sec. for 2 cases, 0.16 sec. for 2 cases, and 0.17 sec. for 1 case. Abnormal ventricular gradient was observed in 3 patients; in 2 of these it was the abnormality of direction, and in the third, of both length and direction. Of these 3 patients showing additional cardiac enlargement the former 2 were in congestive heart failure (Table VI).

As described by Grishman,[13,14] the QRS loop of left bundle branch block is situated to the left and posteriorly; its direction of inscription is clockwise in horizontal view, clockwise in right sagittal view, and counterclockwise in frontal view. Results identical to Grishman's description were obtained in the present study. It must be admitted here, however, that the 2 cases observed had their centripetal limbs and centrifugal limbs partially crossed to each other in frontal view. The QRS loops were open.

The T loop was situated to the right and anteroinferiorly in 7 cases, and to the right and anterosuperiorly in 1 case. Thus, it was situated in a position almost opposite to the QRS loop, showing the following configurations: In horizontal view the T loop showed a clockwise inscription in 3 cases, a counterclockwise inscription in 1 case, and a rod-shaped inscription resulting from superposition of the centrifugal and centripetal limbs in 4 cases. In right sagittal view it showed a clockwise inscription in 6 cases, and a rod-shaped inscription in 2 cases. In frontal view it showed a counterclockwise inscription in 6 cases, and a rod-shaped inscription in 2 cases (Figs. 9 and 10; Table VI).

Accordingly, except for one case (Patient T. K. in Table VI), which showed an adverse inscription between the QRS loop and the T loop in horizontal view, no conspicuously adverse inscription between them was observed throughout all 8 cases. The 3 cases which showed cardiac enlargement and abnormal ventricular gradient showed even the same direction of inscription between the QRS loop and T loop or rod-shaped T loop. On the contrary, in the case which showed an adverse inscription between the QRS loop and the T loop the patient (Patient T. K.) was without a sign of cardiac incompetence, and his ventricular gradient was within normal range, although he suffered from a combined valvular disease and a slight cardiac enlargement. It is interesting to note that the QRS duration in this case was 0.13 sec., which is the shortest for the 8 cases tested.



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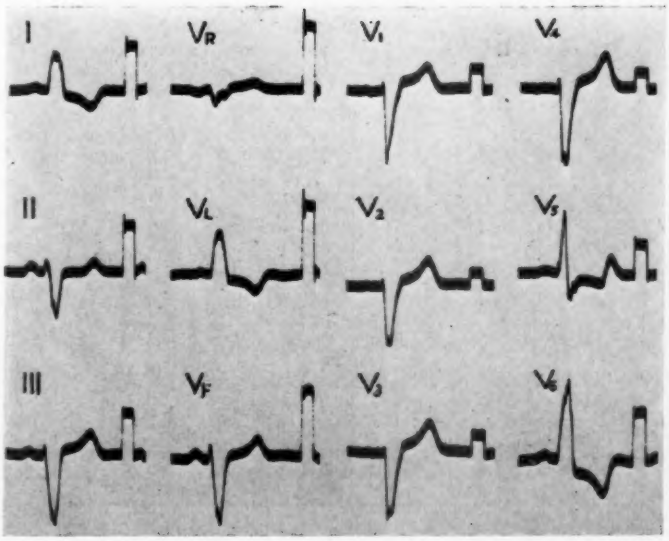


B.

Fig. 9.—Patient S.N., a 68-year-old man with arteriosclerotic heart disease and LBBB. *A*, Whole figure of QRS loop and T loop. *B*, Electrocardiogram.

TABLE VI. DIRECTION OF INSCRIPTION OF T LOOP AND SOME CLINICAL DATA IN CASES OF LEFT BUNDLE BRANCH BLOCK

PATIENT	CLINICAL DIAGNOSIS	DIRECTION OF INSCRIPTION OF T LOOP			ADVERSE INSCRIPTION BETWEEN QRS LOOP AND T LOOP			CARDIAC ENLARGEMENT	CARDIAC INCOMPETENCE	QRS DURATION (SEC.)	VENTRICULAR GRADIENT		
		H	S	F	H	S	F				LENGTH (μV SEC.)	DIRECTION (DEGREE)	ABNORMALITY
S. N.	Coronary sclerosis	C	C	CC	−	−	−	+	+	0.16	73	−72	+
T. Y.	Coronary sclerosis	C	C	CC	−	−	−	+	+	0.14	8	−168	+
M. H.	Coronary sclerosis with high lateral infarction	R	C	CC	−	−	−	+	±	0.16	24	42	−
T. T.	Coronary sclerosis	R	C	CC	−	−	−	+	±	0.15	24	68	−
Y. M.	Coronary sclerosis	R	R	R	−	−	−	+	−	0.17	106	−28	+
T. K.	Combined valvular disease	CC	C	CC	+	−	−	+	−	0.13	74	76	−
T. Y.	Coronary sclerosis	C	C	CC	−	−	−	−	−	0.15	20	16	−
T. A.	Coronary sclerosis	R	R	R	−	−	−	−	−	0.14	34	44	−

C: Clockwise. CC: Counterclockwise. R.: Rod-shaped.

TABLE VII. DIRECTION OF INSCRIPTION OF T LOOP OF VENTRICULAR PREMATURE BEAT AND VENTRICULAR GRADIENT IN CASES WITH VENTRICULAR PREMATURE BEAT

PATIENT	VENTRICULAR PREMATURE BEAT										NORMAL BEAT			
	DIRECTION OF INSCRIPTION OF T LOOP			DIRECTION OF INSCRIPTION OF QRS LOOP			QRS DURATION (SEC.)	VENTRICULAR GRADIENT			VENTRICULAR GRADIENT			OTHER ABNORMAL FINDINGS IN ECG
	H	S	F	H	S	F		LENGTH (μV SEC.)	DIRECTION (DEGREE)	ABNORMALITY	LENGTH (μV SEC.)	DIRECTION (DEGREE)	ABNORMALITY	
Y. M.	R	R	CC	8	C	CC	0.16	24	75	−	18	−29	+	Myocardial change; RBBB
T. A.	R	C	CC	C	C	CC	0.14	36	60	−	19	40	−	Myocardial change
B. I.	R	R	CC	CC	C	CC	0.12	10	5	−	58	14	−	Myocardial change
R. H.	R	R	R	8	8	CC	0.15	24	75	−	25	0	−	Myocardial change
K. M.	R	R	CC	8	C	CC	0.17	36	−6	+	48	36	−	−
T. O.	R	R	R	CC	C	C	0.13	7	−32	+	78	84	−	−
Y. N.	C	CC	C*	C	8	CC*	0.12	19	3	−	63	60	−	−
S. T.	R	C	CC*	C	C	C*	0.13	50	72	−	33	52	−	−
R. H.	CC*	C	CC	C*	C	CC	0.13	89	22	−	65	4	−	−
Y. T.	CC	C	R	CC	C	CC	0.13	87	52	−	47	20	−	−
Y. K.	CC	R	R	CC	C	CC	0.13	27	15	−	24	52	−	−
S. S.	R	R	R	CC	C	CC	0.12	32	22	−	54	44	−	−
Y. Y.	R	R	CC	CC	C	CC	0.11	12	14	−	64	12	−	−
H. H.	R	R	CC	CC	C	CC	0.15	24	38	−	28	63	−	−

*Obviously adverse inscription between the QRS loop and the T loop.
C: Clockwise. CC: Counterclockwise. R: Rod-shaped. 8: Figure-of-eight.

T LOOP OF VENTRICULAR PREMATURE BEAT

The clinical diagnoses have already been described for 14 cases in which there were ventricular premature beats of right ventricular origin. It was disclosed that the ventricular gradient of the QRS-T complex in the basic rhythm in these cases was within a normal range, except for one case which showed myocardial change and right bundle branch block. The ventricular gradient of the ventricular premature beat was within normal range, except for 2 cases in which the ECG showed no pathologic findings except ventricular premature beats (Table VII).

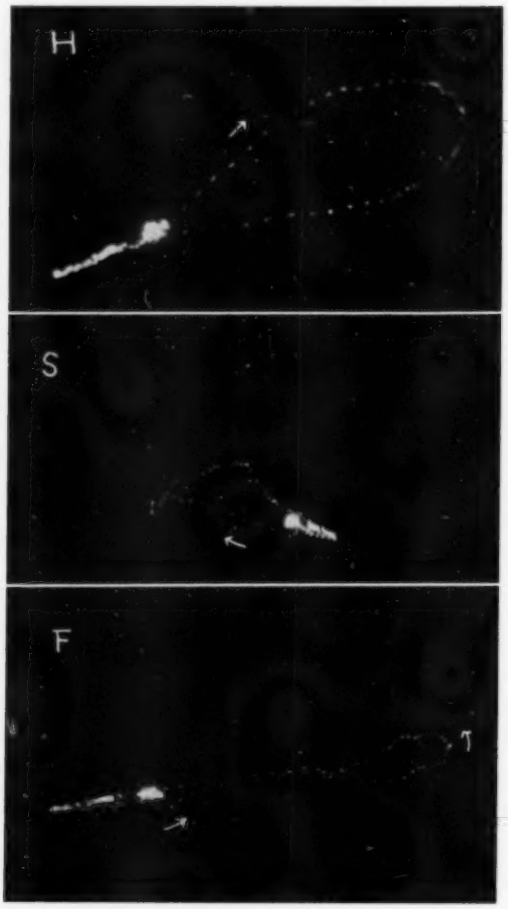


Fig. 10.—Patient T. A., a 64-year-old man with arteriosclerotic heart disease and LBBB. Whole figure of QRS loop and T loop.

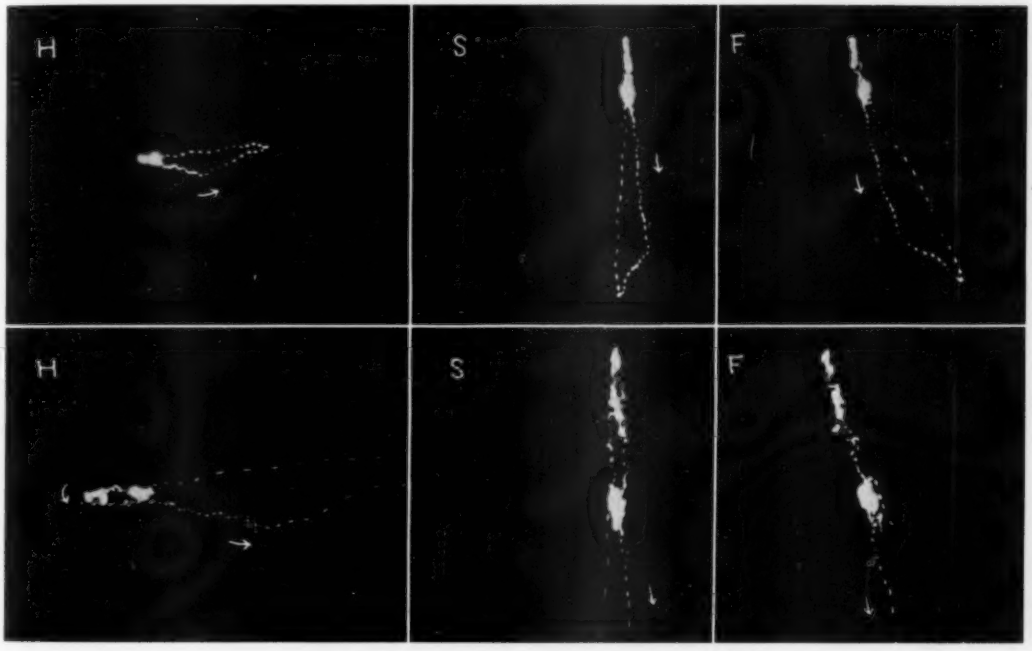
The orientation of the QRS loop of a ventricular premature beat to the origin, in all of the cases, was roughly as follow: left and anterosuperior in 1 case, left and anteroinferior in 4 cases, left and posterosuperior in 5 cases, and left and posteroinferior in 4 cases.

The direction of inscription of the QRS loop in these cases was as follows: clockwise in 4 cases, counterclockwise in 7 cases, and figure-of-eight in 3 cases in

horizontal view; clockwise in 12 cases and figure-of-eight in 2 cases in right sagittal view; clockwise in 2 cases and counterclockwise in 12 cases in frontal view.

Generally, the configuration of the QRS loop is narrow in horizontal view and right sagittal view, and rather wide in the frontal view.

The T loop of the ventricular premature beat of these cases was situated to the right of the origin, almost opposite to the QRS loop. But in 2 cases it had its portion even extended left of the origin.



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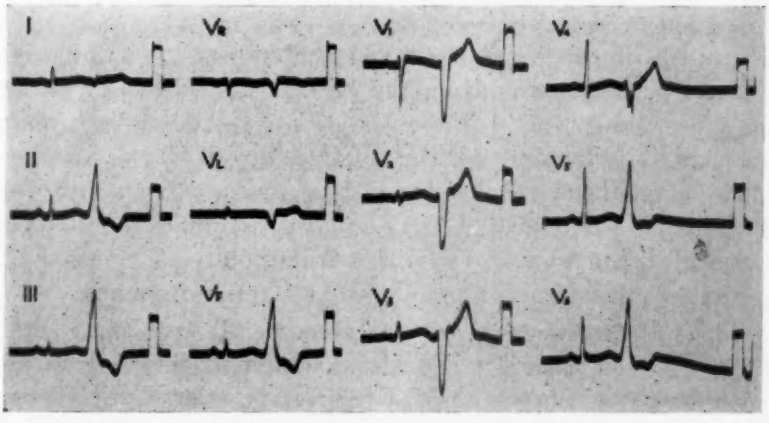

C.

Fig. 11.—Patient Y. K., a 52-year-old woman without any sign of heart disease, except ventricular premature beat. *A*, VCG of ventricular premature beat. *B*, The vicinity of the origin and T loop recorded at higher amplification. *C*, Electrocardiogram.

In horizontal view the T loop showed a clockwise direction of inscription in 1 case, and a counterclockwise direction of inscription in 3 cases, but it was rod-shaped in 10 cases; only 1 case (Patient R. H. in Table VII) showed an adverse inscription between the QRS loop and the T loop, i.e., a case in which the T loop had a portion situated to the left as well as to the right of the origin.

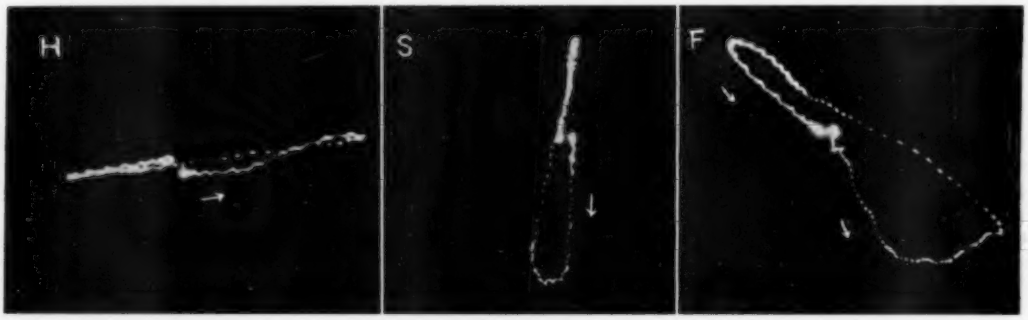

Fig. 12.—Patient K. M., a 53-year-old man with diabetes mellitus. VCG of ventricular premature beat.

In right sagittal view the T loop showed a clockwise direction of inscription in 4 cases, a counterclockwise direction in 1 case, and a rod-shaped direction in 9 cases. No adverse direction of inscription was observed between the T loop and the QRS loop. In frontal view the T loop showed a clockwise direction of inscription in 1 case, a counterclockwise direction of inscription in 8 cases, and a rod-shaped direction in 5 cases (Figs. 11 and 12).

Thus, out of 14 cases with ventricular premature beats, 3 showed an adverse direction of inscription between the T loop and the QRS loop. Throughout these cases an adverse inscription was observed in only one plane of projection. Therefore, no obviously adverse inscription between the QRS loop and T loop was observed in any case, if these exceptional cases are excluded.

DISCUSSION

An advantage of the VCG is that it enables one to differentiate patterns which could not be differentiated on the ECG. For example, the rsR′ pattern on the right precordium can be differentiated into right bundle branch block and right ventricular hypertrophy[19] on the VCG; left axis deviation into horizontal heart and left ventricular hypertrophy on Kimura's vector.[3] Thus it is expected that those findings on ST-T which have so far gone undifferentiated on the ECG will be disclosed on the VCG. From this standpoint, an attempt at vectorcardiographic analysis of left ventricular strain pattern was made.

The T loops of 148 cases showing left ventricular strain pattern or a transitional pattern between normal pattern and left ventricular strain pattern were classified into five types on the basis of their orientation and configuration.

The T loop of Type I, although it was still situated to the left and inferiorly, was found to protrude right anteriorly and inferiorly to the QRS loop, and its direction of inscription was counterclockwise in horizontal view, clockwise in

right sagittal view, and counterclockwise in frontal view. As described above, the direction of inscription of the QRS loop in left ventricular strain pattern was, for most cases, counterclockwise in horizontal view, clockwise in right sagittal view, and counterclockwise in frontal view. Accordingly, the T loop of Type I kept the same direction of inscription as the QRS loop in each of three plane projections. The J vector was observed in almost half the cases. The rest of the cases showed no clear J vector because of halation in the vicinity of the origin. Transitional patterns in the electrocardiogram generally correspond to this type.

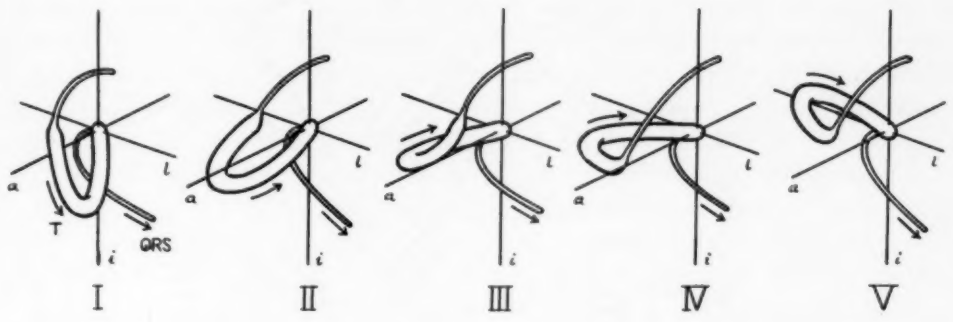

Fig. 13.—Each stage of serial changes of T loop in left ventricular strain (solid view). *l* = left; *a* = anterior; *i* = inferior.

The T loop of Type II lay to the right, almost opposite to the QRS loop. Its direction of inscription was the same as that of Type I, showing the same direction of inscription as the QRS loop. The J vector was observed clearly in most cases of this type. The T loop of Type III in most cases showed an adverse direction of inscription to the QRS loop in horizontal view. As to Type IV the direction of inscription even changed to clockwise in frontal view. Thus, the T loop showed an adverse direction of inscription to the QRS loop not only in horizontal view but also in frontal view. As to Type V the direction of inscription changed to counterclockwise in right sagittal view, showing a direction of inscription adverse to the QRS loop in each of three plane projections. Except for the above-mentioned five types, there were no transitional figures which appeared to be transformed directly from a normal figure to these types. It is assumed therefore that these five types indicate serial stages of the T-loop changes of left ventricular strain pattern. It strongly supports the consideration that the T loop of left ventricular strain pattern changes through this sequence from Type I to Type V.

Spatially, the T loop protrudes right and anteriorly to the QRS loop at first, with the centrifugal loop of the T loop situated right and anteriorly to the centripetal loop. Then, the T loop shifts rightward, passing in lower front of the origin (in upper front in some cases), and reaches right and anteroinferiorly, twisting around its own long axis clockwise in the view from the tip, and finally right and anterosuperiorly (Fig. 13). Here it seems that the torsion around the long axis begins from the tip.

Therefore it seems reasonable to consider that the above-mentioned five types are nothing more than plane projections of various stages during the progression of the T-loop change, and that these types show various grades of the serial changes of the T loop. Thus, hereafter, Grades I-V will be used instead of Types I-V (Fig. 14).

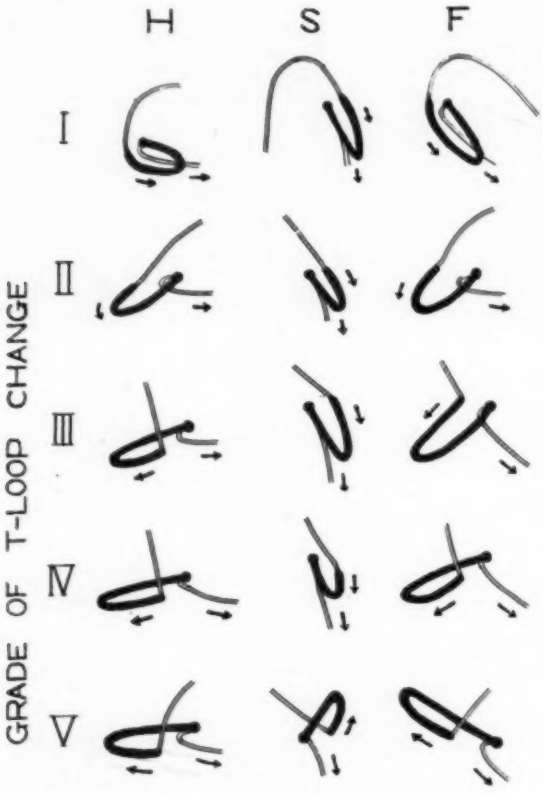

Fig. 14.—Three plane projections of T loop showing change of each grade. The white curves indicate QRS loops; the black curves indicate T loops.

There are slight variations even in the figures of left ventricular strain pattern which do not allow one to differentiate the degree of abnormalities, except for some transitional forms. But in VCG these variations can be systematized into the serial process from a spatial point of view. This is an advantage of VCG over ECG.

Grishman[13] reports that the T loop in left ventricular hypertrophy is situated to the right and anteriorly and sits opposite to the QRS loop. His implication seems to correspond to Grades II-V described in this paper. Grade I is a transitional form.

Even in Kimura's system the T loop is found to make serial changes. Here the T loop shifts rightward, passing in upper front of the origin; and its torsion around its own long axis goes on counterclockwise in the view from its tip. But the T loop in the Kimura vector changes in some cases in a manner similar to that in the Grishman vector. These findings were reported at the 19th Annual

Meeting of the Japanese Circulation Society.[20] They were simultaneously reported also by Inuzuka and Kimura.[7,8] Portheine[9] reports independently T-loop changes on Schellong's system. Here the T loop shifts toward the right, passing in lower front of the origin; its torsion around its own long axis goes on counterclockwise in the view from the tip.

Thus, although a serial process of T-loop change is somewhat in its kind subject to the reference system adopted, it is confirmed, at any rate, that left ventricular strain pattern in ECG can be further analyzed by VCG.

As additional information, each QRS loop accompanying the T loop of each Grade is roughly studied. The QRS loop in left ventricular strain is, as it is reported by Grishman[13,14] to be in left ventricular hypertrophy, situated generally to the left, inferiorly and slightly posteriorly; its direction of inscription in most cases is counterclockwise in horizontal view, clockwise in right sagittal view, and counterclockwise in frontal view. The present finding almost corresponds to his description. One of the characteristic feature of the QRS loop in left ventricular strain is that the loop is situated rather posteriorly to the normal QRS loop. This finding is most clearly observed in the horizontal view. In the present study the foregoing results reveal that as the T-loop change progresses from Grade I to Grade III, the direction of the long axis of the QRS loop deviates gradually posteriorly in horizontal view, although this finding is not statistically significant. In Grade IV the direction of the long axis of the QRS loop tends to point more anteriorly than in Grade III; this finding may be due to the comparatively few cases studied. According to Grishman, the long axis of the QRS loop for left ventricular hypertrophy in the horizontal view points posteriorly to $-30°$ or more. But the present cases do not show this pointing of the long axis of the QRS loop so conspicuously as was mentioned by Grishman, e.g., the heart in a case of Grade-V hypertensive heart disease (G. I., a 64-year-old man) weighed 935 grams on autopsy, but the long axis of the QRS loop even in this case pointed to $-16°$.

So far the author's experiences have shown that the direction of the long axis of the QRS loop for healthy men and women of 20 to 30 years of age is $3.6 \pm 0.95°$ and $3.1 \pm 0.96°$, respectively.[21] Thus, in general, for the Japanese the long axis of the QRS loop in the horizontal view does not point so posteriorly as in Grishman's data. Although this difference is left unexplained, it may be attributable to the fact that the Japanese have a shorter sagittal diameter of thorax than Americans, or to the fact that the author's patients are urban dwellers whose sagittal diameter of thorax is shorter than that of a rural population, resulting in a shorter distance between the electrodes of the anteroposterior lead in Grishman's system.

Since the aforementioned grading of T-loop changes seems to express the severity of changes in the myocardium, other clinical findings may reasonably change in correspondence with the T-loop changes. In an attempt to confirm this, a few clinical data will be reviewed.

At first, cardiac enlargement was studied roentgenologically. It seemed that, roughly, cardiac enlargement could be approached by mere transverse, median-left, or long diameter, etc., although the size ratio between heart and

whole body should have been taken into consideration. As progression was made through the types of T-loop changes the cases of large value in transverse diameter increased, although cases of small value were also found. This was true also with median-left, long diameter, etc. But 3 cases were seen in which transverse diameter exceeded 20 cm., although the T-loop changes in these cases were classified as Grade II. This finding is to be explained later.

It is generally understood that patients with ST-T changes in the ECG have a poor prognosis, while ST-T changes in the ECG do not always mean cardiac incompetence. In this light, a study was made of a possible relationship between T-loop change and the development of cardiac incompetence. As mentioned above, the development of cardiac incompetence increases with the progression of T-loop changes; nearly half the cases of Grade V were found to have cardiac incompetence. These findings seem to support the serial grading of T-loop change as indicating advancing myocardial changes.

Thus, from these observations that the T loop undergoes the changes serially from Grade I to V, and that these grades are parallel with other clinical states, the following conclusion is made on a clinical basis: In left ventricular overloading the T loop undergoes changes in a certain sequence, and the orientation and configuration of the T loop enables one to conjecture the severity of the clinical states.

At an early period of study in VCG, Kimura[3] tried a vectorcardiographic analysis of myocardial changes on his lead system and stated that those cases in which the T loop revealed many protrusions from the QRS loop and/or many inscriptions of a direction adverse to the QRS loop on three plane projections had a poor prognosis. It is presumed that these cases included many instances of left ventricular strain pattern. In the present study it is made clear that the protrusion of the T loop from the QRS loop and its inscription in a direction adverse to the QRS loop develop with a certain order. Portheine[9] observed that a T loop with torsion in the frontal view in Schellong's system showed a high incidence of cardiac incompetence. This observation was studied further in the present experiment, using three plane projections of Grishman's system.

It is a general belief that the degree of pathologic change cannot be ascertained from the amplitude and form of the ST-T deviation in the ECG. In spite of this belief it is understood that the T-loop change in the VCG is parallel with clinical states. Thus, VCG is accredited for its clinical applicability.

Generally, the amplitude in the ECG for healthy human beings shows a broad range of variation, and it is subject to extracardiac factors. On the other hand, the orientation and configuration of the T loop in VCG is based not on the absolute value of the amplitude in component leads, but on differences of amplitude and phase differences among component leads. Therefore it may reflect myocardial changes better, with a comparative elimination of variable factors.

Portheine,[9] using Schellong's system, made a comparative study between VCG and clinical data and stated that a discordant T loop without torsion in the frontal view was subject to the influence of mere ventricular hypertrophy, and that those cases with torsion were under the influence of anoxia of the myo-

cardium. Here it is to be noted that one of the methods of detecting changes in the myocardium itself in the ECG is the ventricular gradient. In this light the relationship between T-loop change and ventricular gradient is to be reviewed. Grishman[13] also suggests an analysis of the VCG on the basis of ventricular gradient. In the present study a statistical relationship existed between the abnormalities of T-loop change and the ventricular gradient, as mentioned above. Now it must be admitted in this relationship that the larger ratio of abnormal ventricular gradient in the cases of Grade I over those of Grade II may have been due to the comparatively small number of cases or to the misclassification of other types of myocardial changes in the category of early left ventricular strain.

The T-loop of left ventricular strain pattern is interpreted as follows: When the T loop is situated opposite to the QRS loop and is inscribed in the same direction as the QRS loop on plane projections, it corresponds to secondary T-wave change; an additional development of the torsion of the T loop (inscription of the T loop contrary to the QRS loop on plane projection) corresponds to a participation of primary T-wave change.

Although the pathogenesis of left ventricular strain pattern is a matter of controversy, a probable theory is the following[22,23]: Because of hypertrophy of the ventricular wall, the net direction of the process of myocardial repolarization becomes the same as that of depolarization; viz., left ventricular strain pattern is considered fundamentally to be a secondary T-wave change as well as the ST-T change of bundle branch block and ventricular premature beat. If Schaefer's[24] expression is adopted, "elementarer Erregungsrückgang" becomes large, and plays a dominant role in the formation of T, and the direction and length of "elementarer Erregungsrückgang" mainly govern the direction and length of T. Thus, if the early depolarized part of the myocardium is repolarized early and the late depolarized part is repolarized late, a general anticipation in VCG is that the first half portion of the T loop will be oriented opposite to the first half of the QRS loop, and that the latter half of the T loop will be situated opposite to the latter half of the QRS loop. Accordingly, it is presumed that the T loop is discordant with the QRS loop and that these loops are of the same direction of inscription on plane projections. This assumption corresponds with the present findings in Grade II, wherein cases of abnormal ventricular gradient are rather rare, although in Grade I, which is considered to be a transitional form, some cases of abnormal ventricular gradient may be found.

As mentioned above, secondary T-wave change in the ECG is expressed in the VCG as a T loop situated opposite to the QRS loop and showing no torsion, and the torsion of the T loop developing under this condition represents an additional indication of primary T-wave change. Here arose the interesting question of what is the vectorcardiographic behavior of the T of left bundle branch block and the T of ventricular premature beat, which are considered to be intensive secondary T-wave changes. Hence, these T loops were comparatively studied with those of left ventricular strain pattern.

In 7 of 8 cases of left bundle branch block, although the clinical states were mostly unfavorable and/or an abnormal ventricular gradient was present,

the T loops situated opposite to the QRS loops showed the same direction of inscription as the QRS loops, or were long and rod-shaped, and thus demonstrated no obviously adverse direction of inscription to the QRS loops. Wenger[25] also reported that the T loop of left bundle branch block is usually inscribed in the same direction as the QRS loop. Even in another case which showed adverse direction of inscription between the QRS loop and the T loop, this feature was demonstrated only in one plane projection. Now, in this case the clinical state was favorable and the ventricular gradient was within normal range, but the QRS duration in the ECG was 0.13 sec., which is rather short for complete left bundle branch block, so that the T-loop change may not have demonstrated an obviously characteristic feature of the T-loop change in left bundle branch block.

A study was also made of 14 cases with ventricular premature beats of right ventricular origin. Of these cases, 11, including 4 cases which even showed findings of myocardial changes in the QRS-T complex in basic rhythm and/or abnormal ventricular gradient, revealed no adverse direction of inscription of the T loops to the QRS loops while they were situated opposite to the QRS loops. Even in 3 cases in which the T loops showed the inscription of an adverse direction to QRS loops this kind of inscription was found only in one plane projection. Those 3 cases which showed an adverse direction of inscription between the QRS loop and the T loop had, paradoxically, a normal ventricular gradient and no sign of heart disease. But the QRS durations in these cases were 0.12, 0.13, and 0.13 sec., respectively, which are rather short for ventricular premature beats. This occurrence is similar to that of left bundle branch block.

After all, the T loop of left bundle branch block and that of ventricular premature beat of right ventricular origin show, with some exceptions, the same direction of inscription as the QRS loop, or a rod-shaped inscription, and never demonstrate a clear torsion, the T loop being situated opposite to the QRS loop. As to the present exceptional cases, it is considered that, since "elementarer Erregungsrückgang" in these cases was not so large because the QRS duration was not so long, a characteristic feature which corresponded to secondary T-wave change had not yet fully developed on the T loop.

Unlike cases of left ventricular strain pattern, cases of left bundle branch block and cases of ventricular premature beats reveal no inscription of an adverse direction between the QRS loop and the T loop, even though the clinical states are unfavorable and/or abnormal ventricular gradients are present. This may be due to the assumption that "elementarer Erregungsrückgang" of these cases is extremely large, so that even the summation of the vector corresponding to the primary T-wave change on it remains the length and direction of T, which is a resultant vector, akin to the "elementarer Erregungsrückgang." (According to general laws of vector calculus, when the larger vector and the smaller vector are vectorially summarized, a resultant vector comes near to the larger vector.) Such occurrence is sometimes encountered as an exception even in left ventricular strain pattern. For example, the above-mentioned 3 cases of Grade II with aortic regurgitation of over 20 cm. of Tr (H. S., a 25-year-old man; K. K., a 61-year-old man; N. Y., a 39-year-old man) were cases of congestive heart failure. Because of such clinical conditions the T-loop change was expected to be

of a high grade; nevertheless, it was Grade II. This can be explained by the fact that the QRS duration of these cases was 0.13 sec., which is comparatively long for left ventricular hypertrophy, and leads to the explanation that influences of secondary T-wave change may be great enough to mainly govern the configuration of the T loop. Furthermore, a case of Grade V (Y. K., a 70-year-old man with arteriosclerotic heart disease) demonstrated the T-loop change approaching Grade III as the left-sided failure proved marked in the clinical course. This may have been due to the fact that $\angle \hat{A}_{QRS}$ changed from $-38°$ to $-55°$, i.e., an increase in left axis deviation developed, and because of its subsequent secondary effects a paradoxical development appeared.

Thus, from the findings in left ventricular strain pattern, left bundle branch block, and ventricular premature beat of right ventricular origin the following conclusions have been reached: The T loop corresponding to secondary T-wave change is situated opposite to the QRS loop but shows no torsion to the QRS loop; an additional development of torsion of the T loop means a participation of primary T-wave change. But, if secondary T-wave change is marked, its influences overwhelm those of primary T-wave change even in VCG and mainly govern the configuration of the T loop.

One further point must be made, i.e., in the above-mentioned cases the torsion of the T loop is referable to primary T-wave change. But from a wider point of view, primary T-wave change does not always indicate torsion of the T loop. For example, the T loop of coronary T,[20] which is representative of primary T-wave change, does not show torsion so much. Accordingly, it is considered that in order to discuss myocardial changes on a wider basis aiming at a general principle of T loop in VCG, further studies must be made not only on the direction of inscription and orientation of the T loop but also on the details of its configuration as well as its spatial relationships with the QRS loop, etc. Furthermore, it must be mentioned that the direction of a vector based upon secondary T-wave change in right ventricular strain, right bundle branch block, and ventricular premature beat of left ventricular origin is almost the same as the direction of normal T, so that the aforementioned interpretation cannot be applied to these conditions.

SUMMARY

A vectorcardiographic analysis is made of left ventricular strain pattern. The T loop of left bundle branch block and ventricular premature beat of right ventricular origin are also discussed. Grishman's cube system is used.

1. The T loop of left ventricular strain pattern, with a few exceptions, changes in the following order: it starts left inferiorly and shifts rightward, passing in lower front of the origin (in some cases in upper front), and then reaches right and anteroinferiorly, twisting around its own long axis clockwise in the view from its tip, and finally, right and anterosuperiorly.

2. The process described above is divided into the following five grades on three plane projections: *Grade I:* The T loop protrudes from the QRS loop, but it is still situated to the left and inferiorly; its direction of inscription in most

cases is the same as that of the QRS loop. *Grade II:* The T loop is situated opposite to the QRS loop, but it shows the same direction of inscription as the QRS loop on three plane projections. *Grade III:* Additionally, the T loop is inscribed in an adverse direction (clockwise) to the QRS loop in the horizontal view. *Grade IV:* The T loop shows an adverse direction of inscription (clockwise) to the QRS loop in the frontal view as well as in the horizontal view. *Grade V:* The T loop also shows an adverse direction of inscription (counterclockwise) in the right sagittal view as well as in the horizontal and frontal views, i.e., adverse to the QRS loop in all three plane projections.

3. This serial change of the T loop seems to be parallel with other clinical findings.

4. The T loop of left bundle branch block is situated opposite to the QRS loop, and, in general, it either shows the same direction of inscription as the QRS loop or is rod-shaped.

5. The T loop of ventricular premature beat of right ventricular origin is generally situated opposite to the QRS loop; it either is inscribed in the same direction as the QRS loop or is rod-shaped.

6. Throughout left ventricular strain pattern, left bundle branch block, and ventricular premature beat of right ventricular origin the T loop which is situated opposite to the QRS loop and is inscribed in the same direction as the QRS loop corresponds to secondary T-wave change; an additional development of torsion of the QRS loop means a participation of primary T-wave change. But when the influences of secondary T-wave change are overwhelmingly more dominant than those of primary T-wave change, the former come to govern mainly the configuration of the T loop.

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Direct Epicardial Potentials in Right Ventricular Preponderance

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The advent of open-heart surgery for correction of congenital heart lesions offers an exciting and definitive approach to the electrocardiographic identification of right ventricular preponderance. Although the application of direct epicardial electrodes over the various surfaces of the beating heart poses no major technical problems, providing surgical exposure is optimum, surprisingly few studies of the epicardial potentials in heart disease have been carried out.[1-5]

To study more fully the apparent multiplicities of the right precordial QRS patterns described in right ventricular preponderance, and to determine the possible origin of the right ventricular potential, direct epicardial potentials were obtained on fifteen patients with isolated valvular pulmonic stenosis and/or tetralogy of Fallot. These two clinical entities were chosen specifically for this study in order to include only classic examples of anatomic right ventricular hypertrophy.

Correlation of the direct epicardial potentials with the routine unipolar electrocardiogram and the calculated hemodynamic data obtained at the time of cardiac catheterization will be made. Additional electrocardiographic data are presented in an effort to clarify further the identification of right ventricular preponderance by means of conventional electrocardiography.

MATERIALS AND METHODS

An 8-mm. zinc lead alloy electrode connected to the V lead of the unipolar electrocardiograph was applied at predetermined sites over the right and left ventricular surfaces in ten instances of isolated valvular pulmonic stenosis, and in five of tetralogy of Fallot (Fig. 1). An attempt was made to ring the muscular area surrounding and forming the base of the high right ventricular outflow tract (Positions 1, 2, 3) as well as the trabecular and apical surfaces of the right ventricle (Positions 4 and 5), and the apex and posterolateral wall of the left ventricle (Positions 6 and 7). Each epicardial potential was recorded simultaneously with Lead AV_R or Lead III, so as to document time relationships between the activation potentials of both ventricles.

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Utilization of bilateral anterior thoracotomy with transection of the sternum for the surgical correction of the congenital defects greatly facilitated exposure of both ventricular surfaces and, particularly, allowed excellent epicardial mapping of the outflow tract of the right ventricle. The routine clinical unipolar electrocardiogram and the cardiac catheterization data are shown on individual case presentations. Cardiac catheterization was carried out preoperatively at the Cardiovascular Laboratory, University Hospitals, on thirteen of the fifteen patients. Right ventricular pressures were measured at the time of surgery in the other two patients. Individual case presentations will demonstrate the applicability of predicting a high ventricular workload ratio,* thereby implying right ventricular hypertrophy, by the identification of a predominant late R wave in Lead AV_R with vertical cardiac position.[6]

All direct epicardial electrocardiograms were obtained on a Sanborn Twin-Beam at paper speeds of 25 and 50 mm. per second. Because of the considerable epicardial electromotive potential, all recordings were attenuated 4 or 10 times in order to facilitate recording.

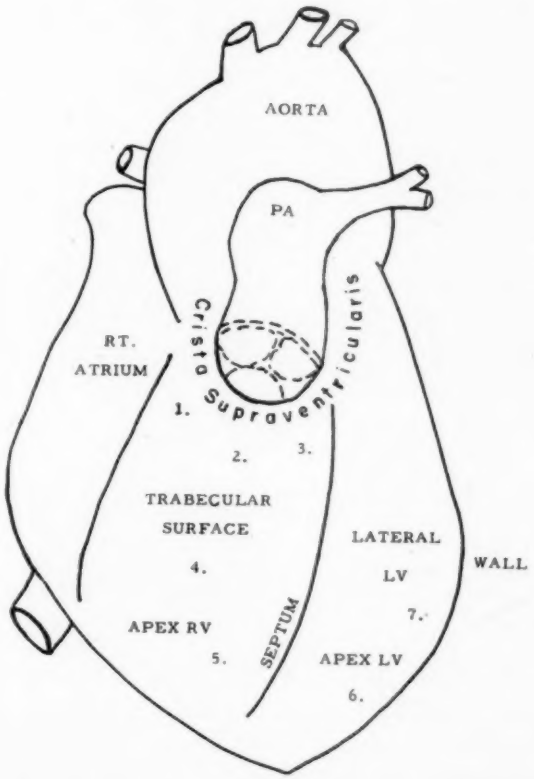

Fig. 1.—Sites for epicardial potentials. Positions *1*, *2*, and *3* ring the muscular area surrounding and forming the base of the high right ventricular outflow tract. Positions *4* and *5* are located over the trabecular and apical surfaces of the right ventricle, respectively, while position *6* is over the anterior apex of the left ventricle, and position *7* overlies the posterolateral surface of the left ventricle.

RESULTS

The electromotive potential recorded at positions 1 or 2 consisted of a distinct rR′ pattern in twelve patients, an apparent slurred R wave in two, and

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***Ventricular workload ratio is determined by dividing the right ventricular work index by the left ventricular work index. Normal range is 0.020 to 0.030. A rising right ventricular work index is reflected in an increasing ventricular workload ratio approaching, or exceeding, unity.**

an apparent qR complex in one. Of considerable interest was the consistent finding of an rS or RS potential at positions 4 and 5, i.e., the trabecular or free wall of the right ventricle. Position 6 consistently yielded an initial septal q wave, with a diphasic QRS complex; position 7 revealed excellent left ventricular potential. This latter finding was significant because of the presence of diminutive left ventricular potential in the left precordial leads of the clinical electrocardiogram.

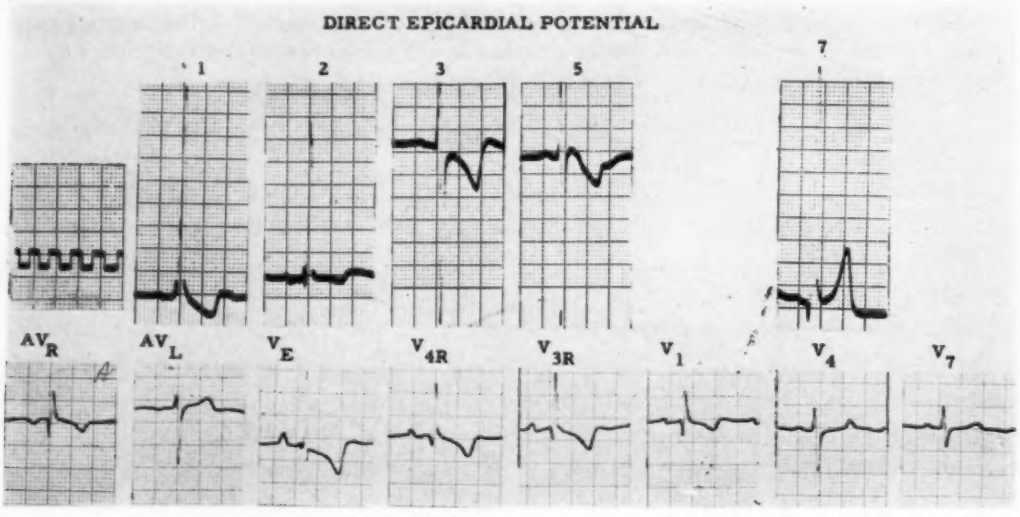

Fig. 2.—W. J., 37 years old. Valvular pulmonic stenosis.

R.A. = M: 6 mm. Hg	C.I. = 2.8 L./min.
R.V. = 94/3.0 mm. Hg	RVWI = 3.05 Kg./min./M.^{2}
P.A. = 18/6 mm. Hg	LVWI = 3.70 Kg./min./M.^{2}
M: 14 mm. Hg	VWLR = 0.82
R.F.A. = 126/77 mm. Hg	

The distinct rR′ pattern at epicardial positions 1 and 2 is quite similar to that seen over the ensiform process (V_E) on the conventional electrocardiogram. Note the apparent qR pattern in the right precordial leads V_{4R}, V_{3R}, and V_1.

The similarity of the right precordial chest leads to the direct epicardial potential at positions 1 and 2 was quite striking. In three instances an apparent initial q wave was seen in the right precordial chest leads V_1, V_{3R}, and V_{4R}; yet, V_E revealed a distinct rR′ pattern which was reproduced in entirety at positions 1 and 2 (Fig. 2). In two patients an apparent pure R wave in Leads V_1 and V_E was depicted as a more distinct rR′ pattern in Lead V_{3R}, as well as at epicardial position 1 (Fig. 3). In a single patient an apparent qR pattern was identified in Lead V_1, and a similar finding was present at epicardial positions 1 and 2, with only a suggestion of a poorly defined initial R wave at position 1 (Fig. 4). Fig. 5 reveals an apparent pure R wave in Lead V_1, with a distinct rR′ pattern in Lead V_E, and an absent late predominant R wave in Lead AV_R. A distinct rR′ pattern was identified at epicardial positions 1 and 2. Figs. 6, 7, and 8 all revealed classic patterns of right ventricular preponderance on the routine clinical electrocardiogram, with slurred R waves or rR′ patterns in Lead V_1, late predominant R waves in Lead AV_R, and diminutive R waves in the left

ventricular leads. A distinct rR′ pattern was recorded at epicardial position 1 in all three instances. The markedly elevated RST segment identified at epicardial positions 2 and 4 in Fig. 8 was due to the injury potential secondary to transventricular puncture for purposes of recording right ventricular pressures.

DISCUSSION

Origin of the Right Ventricular Potential of Right Ventricular Preponderance.—The current epicardial electrocardiographic potentials recorded over the various surfaces of either ventricle seemingly confirm previous concepts that the tall right precordial R waves seen in right ventricular preponderance arise from the medial base of the high right ventricular outflow tract, and refute the contention that the "classic" electrocardiographic signs of right ventricular hypertrophy

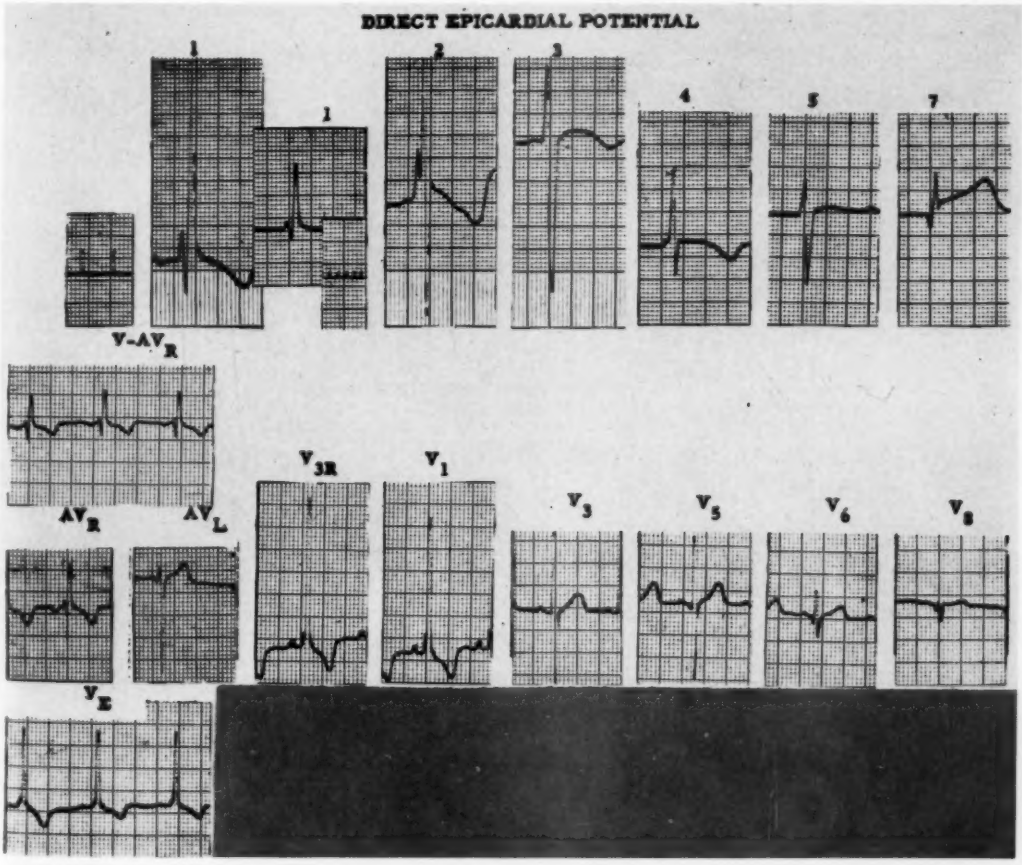

Fig. 3.—J. A., 12 years old. Valvular pulmonic stenosis.

R.A. = M: 10 mm. Hg	RVWI = 4.2 Kg./min./M.^{2}
R.V. = 135/—5.0 mm. Hg	LVWI = 5.0 Kg./min./M.^{2}
P.A. = M: 23 mm. Hg	VWLR = 0.84
F.A. = 122/75 mm. Hg	

The apparent pure R wave identified on V_1 of the conventional electrocardiogram is shown as a more distinct rR′ pattern at V_{3R} and as a slurred R wave at V_E. A distinct rR′ pattern is identified at position 1 on the epicardial study. Note the rS pattern at positions 3 and 5.

are either pure R or qR patterns in the right precordial leads. It appears that these latter two patterns are mere expressions of an rR′ configuration, as earlier suggested by Myers[7] and Morris and Whitaker.[8] The initial septal R wave either is fused on the ascending limb of the apparent pure R wave or is lost in the preceding isoelectric line of the apparent qR complex, inasmuch as distinct epicardial rR′ complexes were identified in twelve of the fifteen patients studied, with a slurred R wave present in two of the three other patients studied. It is felt that meticulous exploration of the medial outflow tract would have resulted in identification of a more distinct rR′ pattern in the two instances of the slurred R wave. We cannot discount the possibility of right-to-left septal depolarization to account for the single instance of an apparent qR complex identified at epicardial positions 1 and 2. Fowler and Helm,[9] Myers,[10] and Kert and Hoobler[11] have previously documented right-to-left septal depolarization in both normal subjects and patients with heart disease.

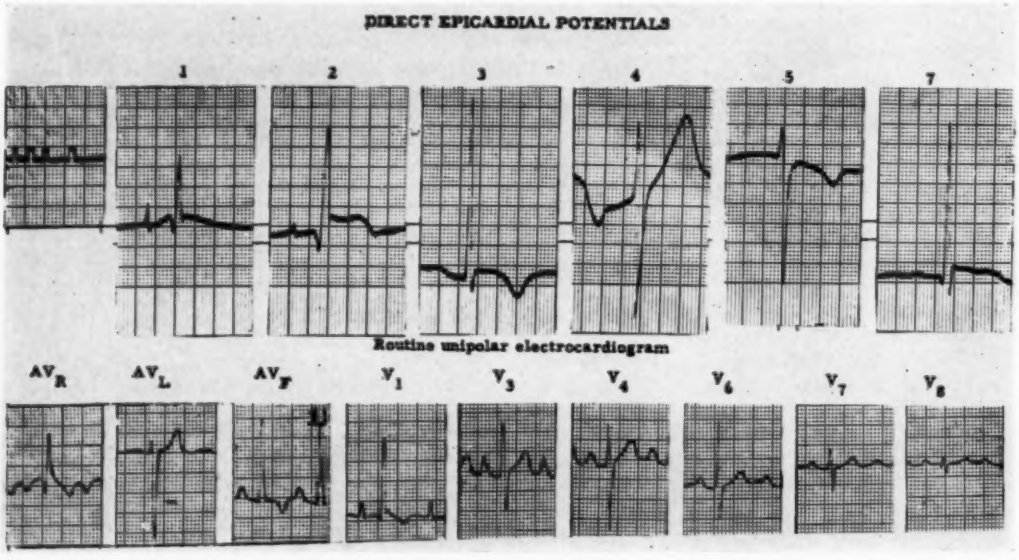

Fig. 4.—C.N., 16 years old. Tetralogy of Fallot (valvular pulmonic stenosis).

R.A. = M: 8 mm. Hg	RVWI = 2.8 Kg./min./M.^{2}
R.V. = 102/20 mm. Hg	LVWI = 3.6 Kg./min./M.^{2}
P.A. = M: 16 mm. Hg	VWLR = 0.77
F.A. = 123/80 mm. Hg	

The apparent qR pattern seen in V_1 of the conventional electrocardiogram is similarly recorded as an apparent qR pattern at positions 1 and 2 on epicardial studies, with only a suggestion of an initial r at position 1.

The Deceptive Incomplete Right Bundle Branch Block Pattern.—Much inconsistency exists in the literature in the attempts to differentiate between the rR′ patterns of the so-called "incomplete right bundle branch block," with or without associated right ventricular hypertrophy, and the rR′ pattern identified with right ventricular hypertrophy, best described by Myers[7] as "delayed activation through the free-wall of the right ventricle." In the latter category, Myers felt that activation of the initial r wave, as measured from the onset of QRS

to the onset of the R′, should be 0.02 second or less, whereas in the so-called incomplete right bundle branch block this measurement should be between 0.03 and 0.04 second. The current data would not make such a differentiation so precise, because the above-noted measurement varied considerably between 0.02 and 0.04 second in all patients studied. Furthermore, on the basis of an analysis of the current data and those of Blount and associates,[5] Walker and associates,[12] and Martins de Oliveira and associates,[13] the term "incomplete right bundle branch block" should be replaced by "the rR′ pattern associated with right ventricular preponderance," since it appears that the R′ configuration identified in the right precordial chest leads is due to late activation of the hypertrophied right ventricular outflow tract, and not to a defect in the right bundle branch system. Walker and associates[12] have suggested that as the degree of right ventricular hypertrophy progresses, the rR′ pattern becomes a pure R wave. That their opinion differs from the current data appears to stem from

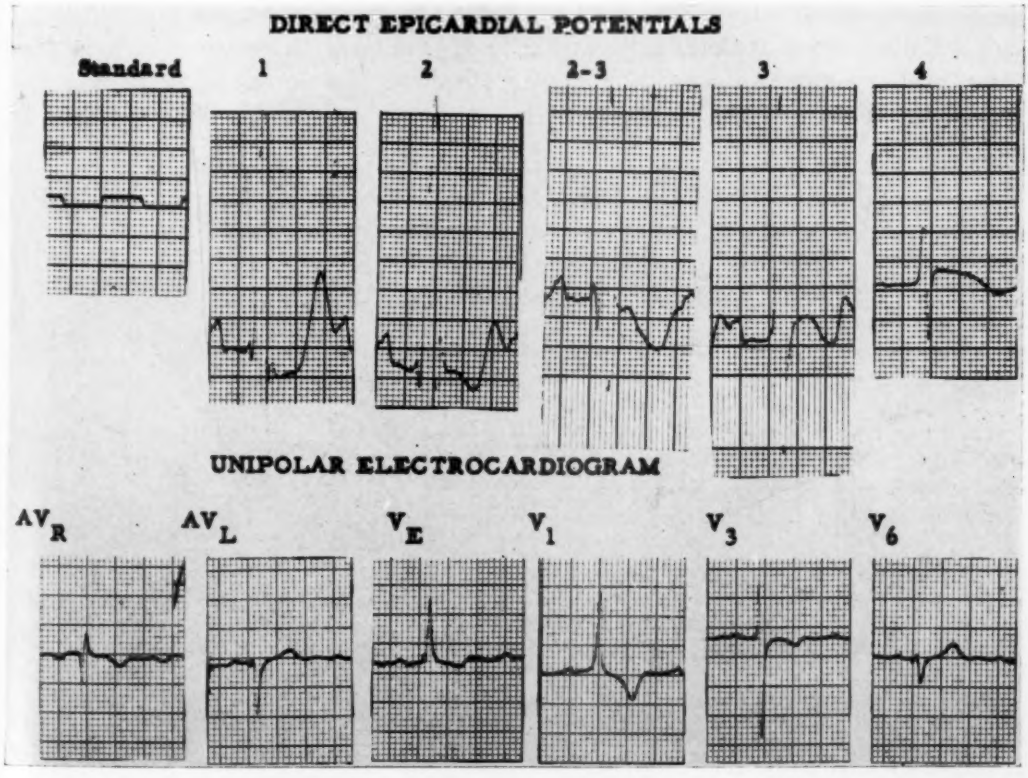

Fig. 5.—R. B., 22 years old. Tetralogy of Fallot.

R.A. = M: 6 mm. Hg
R.V. (low) = 115/3.0 mm. Hg
R.V. (infundibulum) = 75/5 mm. Hg
P.A. = 30/5 mm. Hg
L >R shunt (index) = 1.3 L./min. (No R >L shunt)

RVWI = 3.3 Kg./min./M.^{2}
LVWI = 5.1 Kg./min./M.^{2}
VWLR = 0.64

There is an apparent pure R wave at V_1, with a more distinct rR′ at V_E, and a distinct rR′ pattern at the epicardial sites 1 and 2. Lead AV_R fails to show the predominant late R wave, for here the electromotive potential arising from the hypertrophied right ventricular outflow tract is predominantly reflected laterally and inferiorly rather than superiorly.

those authors' identification of the right precordial QRS complexes, which often presented rR′ patterns, yet were classified as R waves.

Predictions of Fact and Fallacy Established by Epicardial Potentials.—The prediction of Myers[7] that the high outflow tract of the right ventricle (crista supraventricularis) gives rise to the prominent right precordial R waves, and that the trabecular surface or free wall of the right ventricle displays an rS complex has been shown to be fact by the current study. Myers' reasoning apparently stemmed from autopsy findings that right ventricular hypertrophy tends to develop principally or exclusively in the tricuspid ring and/or crista supraventricularis, with the trabecular portion of the right ventricle remaining relatively thin. Although Carouso and associates[3] identified predominant R waves as arising from the right ventricular surface in three patients with tetralogy of Fallot, McGregor[4] found only rS complexes on direct right ventricular epicardial exploration. Unfortunately, McGregor had inserted a wire-tipped electrode blindly through a pericardial slit via a left-sided thoracotomy approach in ten instances of tetralogy of Fallot. From the current observations on direct epicardial potentials it would appear that he did not have access to the high outflow tract of the right ventricle, but rather obtained the potential only over the trabecular surface of the right ventricle. On the basis of his observations, he

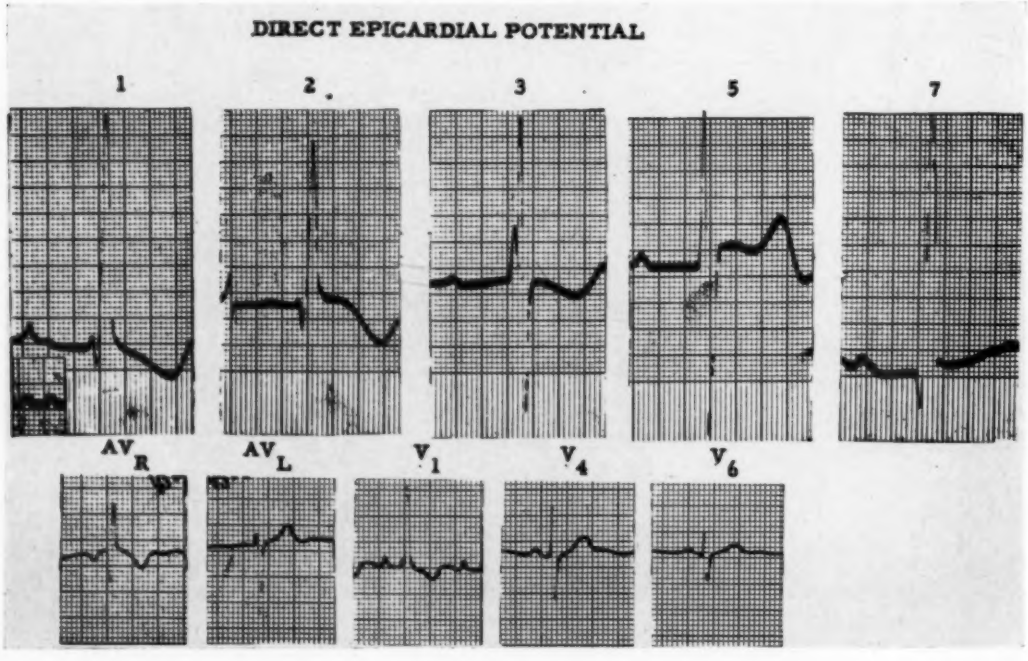

Fig. 6.—S. Y., 17 years old. Valvular pulmonic stenosis.

R.A. = M: 8 mm. Hg	C.I. = 3.9 L./min.
R.V. = 120/0 mm. Hg	RVWI = 4.1 Kg./min./M.^{2}
P.A. = M: 20 mm. Hg	LVWI = 5.4 Kg./min./M.^{2}
B.A. = 128/82 mm. Hg	VWLR = 0.78

The classic pattern of right ventricular preponderance is seen on the conventional electrocardiogram with a distinct rR′ pattern present at V_1 and at the epicardial positions 1 and 2. Note the normal-appearing left ventricular potential identified at epicardial position 7.

felt that he had corroborated the beliefs of Goldberger,[14] Kossmann and associates,[15] and Goodwin[16] that the tall right precordial R waves seen in right ventricular preponderance actually arise from the posteriorly displaced left ventricle. This contention can no longer be considered.

Blount and associates[5] recently studied the right ventricular surface potentials in five instances of atrial septal defect. They found the rSR′ or rSR′s′ patterns as identified in the right precordial electrocardiograms to arise from the outflow tract of the right ventricle just below the pulmonary valve. In a single instance, in which there was gross right ventricular hypertension, a distinct rR′ pattern was shown to arise from an area similar to position 1 in our current study. Herold and Kaindl[2] obtained direct epicardial potentials from the ventricular surface in twenty-one patients. Only four, however, had congenital heart lesions wherein unequivocal right ventricular hypertrophy could be anticipated, namely, pulmonary stenosis (2 patients), tetralogy of Fallot (1 patient), and Lutembacher's syndrome (1 patient). These investigators, too, found rS potentials over the trabecular wall of the right ventricle and more predominant R waves over the high outflow tract. A left-sided thoracotomy approach was utilized in nineteen of the twenty-one patients, thereby limiting epicardial exploration.

More recently, Barbato and co-workers[1,17] have recorded direct epicardial potentials in seventeen normal subjects and in thirty-one patients with established heart disease. Although the right ventricle was not explored in its entirety, the predominant QRS pattern identified over the anterior surface of the right ventricle in normal subjects was an rS complex. However, several instances of rSR′ patterns were documented over the high outflow tract of the right ventricle.

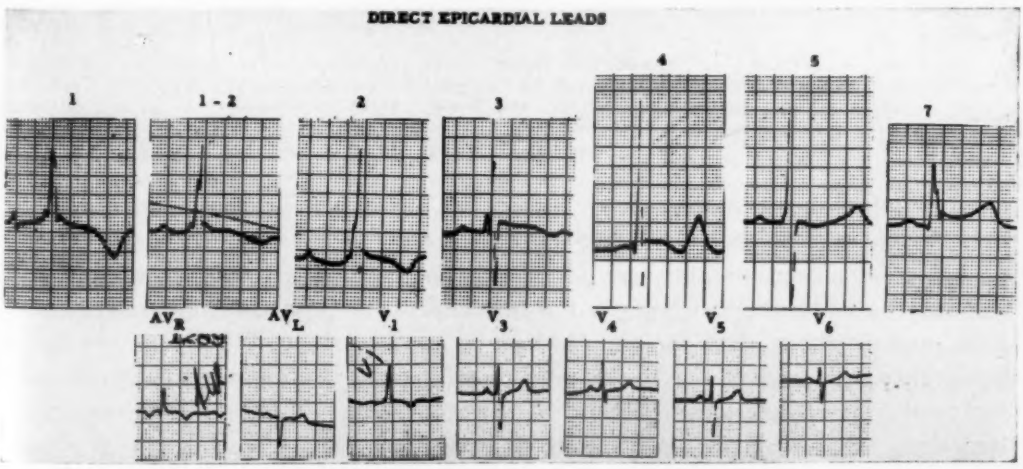

Fig. 7.—M. E., 39 years old. Valvular pulmonic stenosis.

R.A. = M: 6 mm. Hg
R.V. = 126/0 mm. Hg
P.A. = M: 13 mm. Hg
F.A. = 126/72 mm. Hg

RVWI = 5.7 Kg./min./M.^{2}
LVWI = 6.3 Kg./min./M.^{2}
VWLR = 0.88

The conventional electrocardiogram is diagnostic of severe right ventricular preponderance, with a slurred R wave identified at V_1. A distinct rR′ pattern is seen at epicardial positions 1-2 and 2.

Included in the pathologic study were five instances of tetralogy of Fallot and two of pure pulmonic stenosis. Figure 4 (tetralogy of Fallot) of their data revealed a distinct rR′ pattern from an area corresponding to position 2 of our study, and an RS pattern from areas corresponding to our positions 4 and 5. They, too, encountered the problem of inadequate right ventricular exposure, which limited epicardial exploration in all instances.

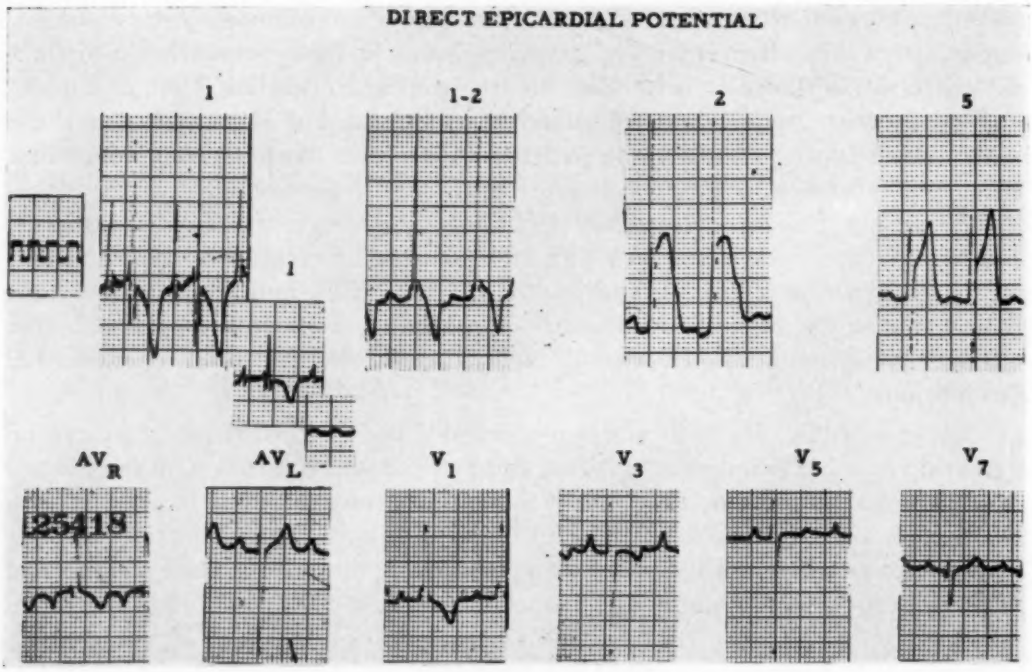

Fig. 8.—C. A., 9 years old. Tetralogy of Fallot. R.V. = 75/5.0 mm. Hg (determined at time of thoracotomy). The slurred R-wave pattern seen at V_1 is readily identified as an rR′ at epicardial position 1, best shown in the attenuated insert. The conventional electrocardiogram is again diagnostic of severe right ventricular preponderance.

Investigation of intracavitary potentials by Schlesinger and co-workers,[18] Sodi-Pallares and associates,[19] Kert and Hoobler,[11] and Kossmann and associates[20] has identified a predominant late R′ wave as the catheter tip was placed near the base of the pulmonary valve in normal hearts. These data seemingly offer additional evidence that the muscle bundle of the tricuspid ring and/or crista supraventricularis gives rise to the predominant right precordial R′ wave of right ventricular preponderance merely by exaggeration of the normal potential by a hypertrophied right ventricular outflow tract.

The Composite Electrocardiographic Pattern of Right Ventricular Preponderance.—In a previous publication it was stressed that there was no single electrocardiographic lead which would unfailingly inscribe existing right ventricular preponderance.[6] Through the analysis of the entire electrocardiogram, however, one is able to detect hemodynamically or anatomically significant right ventricular lesions. Fig. 9 depicts the essentials involved in the pattern of right ventricular

preponderance. An rR′ pattern arising from position A, namely, the high medial outflow tract of the right ventricle, may be subtended to one of three more distinct positions, namely, AV_R, V_{3R}, or V_E. It may be expressed as an rR′ pattern, an apparent slurred pure R wave, or an apparent qR complex. The value of a predominant late R wave in Lead AV_R in assessing existing right ventricular preponderance in the presence of a vertical cardiac position, and in

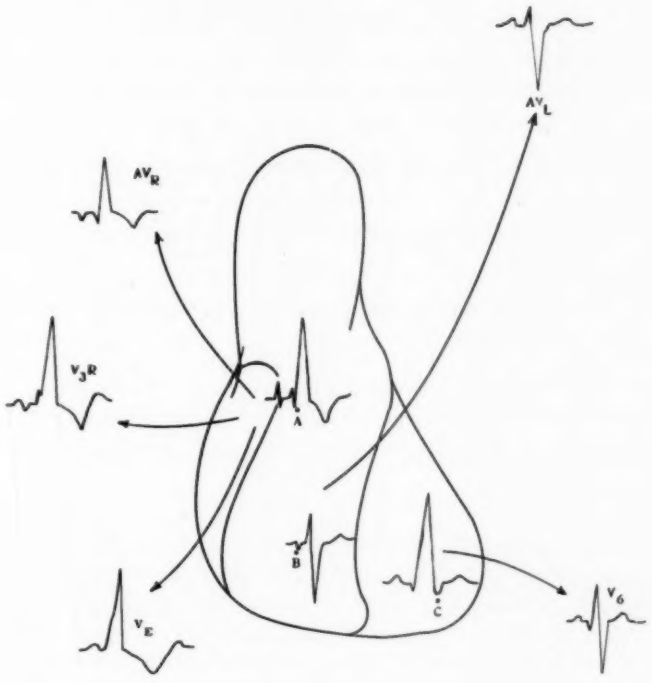

Fig. 9.—Graphic representation of the electromotive potential as seen in right ventricular preponderance. Points *A*, *B*, and *C* represent the epicardial potential recorded at the high outflow tract of the right ventricle, free wall of the right ventricle, and free wall of the left ventricle. The directional arrows depict the electromotive potentials as identified at conventional sites, namely, AV_R, V_{3R}, V_E, AV_L, and V_6.

implying a high right ventricular work index and ventricular workload ratio was documented earlier.[6] Instances occur, however, wherein the rR′ pattern of the right ventricular outflow tract is subtended chiefly to V_{3R} and V_E, and more rarely only to V_E. It is in this latter instance that Lead III of the standard electrocardiogram may give the only clue to an anatomically significant right ventricular lesion by the presence of a distinct rR′ pattern identical to that present in Lead V_E. We have found this to be particularly true in instances of infundibular pulmonic stenosis. The composite electrocardiographic pattern of right ventricular preponderance requires the presence of a qRS or qrS complex in the left ventricular leads in conjunction with the right precordial rR′ pattern. Although normal-appearing qR or qRs complexes are documented over the epicardial surface of the lateral wall of the left ventricle in proved instances of right ventricular hypertrophy, the resultant electromotive potential recorded

over the left anterior chest is the qrS pattern. Finally, the rS pattern identified in Lead AV_L is believed to arise from the trabecular or free wall of the right ventricle. Thus, one can appreciate that the electrocardiographic impression of right ventricular preponderance rests upon an analysis of the entire electrocardiogram.

SUMMARY

1. A distinct rR′ pattern was identified as arising from a relatively focal area of the high medial outflow tract of the right ventricle in twelve of fifteen instances of pure pulmonic stenosis or tetralogy of Fallot, with a slurred R wave occurring in two and an apparent qR pattern in one.

2. Although often presenting as pure R waves or qR patterns in the conventional right precordial electrocardiogram, this rR′ configuration of right ventricular preponderance is subtended to one of three or more positions, namely, superiorly to AV_R, laterally to V_{3R}, or inferiorly to V_E (ensiform process).

3. This rR′ configuration is believed to represent activation of a hypertrophied right ventricular outflow tract, and not an anatomic defect in the right bundle branch system.

4. The electrocardiographic impression of right ventricular preponderance rests upon an analysis of the entire conventional electrocardiogram and not on any single lead.

Appreciation is extended to Dr. G. G. Rowe and Dr. G. M. Maxwell, Cardiovascular Laboratories, University Hospitals, for their invaluable assistance in the tabulation of the hemodynamic data and evaluation of the patients; to Dr. J. K. Curtis and Dr. O. O. Meyer for their help in the final preparation of this manuscript; to Dr. W. E. Gilson for technical advice in recording the epicardial potentials; and to Mrs. Janet C. Lloyd and Mrs. Lila Mulloy for secretarial assistance. All photographic reproductions were made by the Department of Medical Illustrations, Veterans Administration Hospital, Madison, Wis.

ADDENDUM

Since submission of this manuscript, the study of epicardial potentials has been completed on two additional patients with tetralogy of Fallot, and one patient with isolated valvular pulmonic stenosis. A distinct rR′ pattern was identified at epicardial position 1 in all three instances.

The study of epicardial potentials has also been completed on nine patients with ventricular septal defects (five having severe pulmonary hypertension, three having normal right ventricular pressures but with considerable left-to-right shunts, i.e., greater than 4 L./min., and one having normal right ventricular pressure and minimal shunt); on six patients with auricular septal defects (one having severe right ventricular hypertension, two having normal right ventricular pressures with increased left-to-right shunts greater than 5 L./min., and three having normal right ventricular pressures and minimal left-to-right shunts); and in single instances of atrioventricular communis, aortic stenosis, and aortico-right ventricular fistula secondary to rupture of the sinus of Valsalva. Epicardial potentials have also been recorded on two adults who came to thoracotomy for pleural and pericardial decortication, respectively.

A distinct rR′ pattern was identified at epicardial positions 1 or 2 in twelve of the thirteen patients with either gross right ventricular hypertension or large left-to-right shunts. The exception was a 2½-year-old child with a ventricular septal defect and pulmonary hypertension who had a distinct qR complex at epicardial positions 1 and 2.

In the two normal subjects, as well as the isolated instances of aortic stenosis, aortico-right ventricular fistula and ventricular septal defect with a minimal left-to-right shunt, an rSr′ pattern was identified at epicardial positions 1 and 2.

Thus it appears that the rR′ pattern as identified over the high medial outflow tract of the hypertrophied right ventricle is merely an exaggeration of the normal.

Brusca and associates[21] have recently published data on epicardial potentials in fifteen patients with either pulmonary valvular stenosis or variants of tetralogy of Fallot. Predominant R waves over the base of the right ventricle, and rS complexes over the trabecular surface of the right ventricle were recorded.

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Importance of the Unipolar Morphologies in the Interpretation of the Electrocardiogram: The Theoretical Basis of the Unipolar Morphologies and Its Correlation With Vectorial Analysis, With Cardiac Activation, and With the Potential Variations at the Epicardial Surface of the Heart

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For many years an empirical approach has been used in electrocardiographic interpretation. The correlations between electrocardiographic changes and clinical, radiologic, and postmortem findings were systematically looked for. Several electrocardiographic patterns were established for the recognition of specific functional and anatomic changes of the heart. Inasmuch as an electrocardiographic theory did not exist, it was necessary to memorize the morphologies of the most important patterns. Those tracings that did not conform to the patterns described could not usually be interpreted in a satisfactory manner.

The vectorial study in electrocardiographic interpretation has been of great help and it has also contributed to a better understanding of the tracings. This vectorial analysis has become more valid since the investigations on the sequence of auricular and ventricular activation. The vectorial approach has limitations, inasmuch as it is only valid if the electrical phenomenon of the heart is studied with distant electrodes,[1] but it does not explain those morphologies recorded with the electrodes nearer the heart.

Investigations performed[2-5] in the Department of Electrocardiography on the process of activation of the heart have familiarized us with the unipolar morphologies obtained at the epicardial surfaces, at different levels of the ventricular cavities, in the thickness of the free ventricular walls, and in the interventricular septum. These tracings, recorded in the dog's heart in normal or experimental conditions similar to those seen in human hearts, have enabled us to present a new approach in the interpretation of electrocardiograms. This new form of clinico-electrocardiographic interpretation endeavors to explain the morphologies obtained in each lead, the vectors in the different planes and in space, the vectorcardiograms, the notchings, the slurrings, and all the other

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characteristics of the tracing in the function of the sequence of the activation process of the heart. If it is possible to obtain an interpretation using the above-mentioned procedure, we can say that the tracing has been "understood" satisfactorily; on the other hand, if an interpretation is reached, even if this coincides with the clinical diagnosis, but cannot be explained in the function of the activation process of the heart, we simply say that the tracing has not been understood.

In the present paper, only some aspects of electrocardiographic interpretation are discussed, with emphasis on the study of the morphologies recorded by unipolar leads. To justify the analysis of these morphologies, a theoretical concept different from the vectorial one is discussed: Poisson's integral[6] and its implications give a good correlation between the unipolar morphologies obtained at the epicardial surface of the heart and those others recorded at the body's surface through the precordial and limb unipolar leads.

Wilson's exposures explaining the unipolar morphologies[7] have not been accepted by many authors, probably because of the difficult mathematical approach in the study of Poisson's integral. In this presentation we intend to explain in an easy manner the application to the heart of that integral.

METHODS

Two different basic methods are used in the interpretation of the electrocardiograms: (1) the vectorial analysis, and (2) the study of the morphologies in unipolar leads.

1. *Vectorial Analysis.*—The determination of the instantaneous electrical axis and mean electrical axis of auricular and ventricular depolarization and recovery (ÂP, ÂQRS, ÂT, ÂRS-T) in the frontal, horizontal, and sagittal planes, as well as the vectorcardiographic studies in the same planes, have the same physicomathematical foundation: the Stratton theorem and the appliance of the solid angle to the activation fronts.

Stratton's theorem, also called theorem of equivalence,[8] gives a means for determining the potential due to the charges distributed in the heart. The potential due to any distribution of charges, with the net value of the charges equal to zero, could be represented at a distance as the potential due to a dipole called the equivalent dipole. The Stratton theorem must be applied because the vectors representing the charges present in the heart are of the fixed, polar variety. The application of these vectors are fixed to different points, so that they do not lend themselves to elementary operations and the well-known parallelogram law used in vector addition can no longer be applied.

The appliance of the solid angle to the activation fronts is correct, but the double layer must be regarded[9] "as an elastic membrane that snaps into the form of a double-layer disc subtended by its unaltered boundary."

There are experimental reasons to believe that in some few cases the distribution of charges in the heart will not snap into the form of a double-layered disc: ventricular fibrillation, injury tissues, unusual distributions of Purkinje fibers, etc. In these conditions the theorem of equivalence gives a solution while it is difficult to apply the solid angle.

At any rate, using any of the aforementioned mathematical approaches, the result is the same: The charges of the heart could be represented at a distance by a single vector or equivalent dipole. We are confronted with several important questions in relation to the equivalent dipole, and, for the present time at least, only partial solutions in this respect can be given.

First question: What is the position and direction in the heart of the vector that is recognized at a distance as an equivalent dipole?

Recently, Sodi-Pallares and co-workers,[10] with the help of Clinton D. Janney, Ph. D., applied Stratton's theorem to the heart. In that theorem there are several constants which give the position and the moment of the dipole, constants which are contingent upon the prevailing charge distribution. In the mathematical analysis made by Janney it was possible to demonstrate that the equivalent dipole was determined by the centroids of the positive and negative charges of the heart. The moment of the dipole is a vector with its direction going from the centroid of negative charges to the centroid of positive charges. The magnitude of this dipole is as though all of the actual positive charges were gathered together at the centroid of positive charges and all of the negative charges were similarly gathered together at the centroid of the negative charges. (The magnitude of the vector is not limited by the centroids.) This vector is not equivalent to the vectorial summation of all the fixed vectors of the heart.

Second question: Is our knowledge on the equivalent vector sufficient to project it to different planes and leads as we do in electrocardiographic and vectorcardiographic studies?

The experimental work done directly on the heart has been insufficient, and, up to the present time, we disregard the location of the centroids. The experimental studies give us only an approximate correlation between the equivalent dipole studied by distant leads and the sequence of the activation of the heart.

When vectorcardiographic methods or distant leads are used, the electrical field produced by the heart is very similar to that of a dipole in which the magnitude and direction can be easily determined. We do not know, however, if the parameters which defined the distant dipole correspond to the projection of the dipole limited by the centroids in the heart.

Very recently, Sodi-Pallares and associates[10] have found some degree of correlation between the vectorcardiographic loops recorded in the three different planes and a vector limited by the points of the greatest positive (source) and negative (sink) potentials ("maximal potential gradient"). These points are not the centroids, and, although the "locus" of the points with maximal positive and negative potential is very close to the centroids, the maximal potential gradient must not be confused with the equivalent dipole.

There are still a great many problems to be studied in order to justify the physical basis of the single vector theory. At the present time we simply accept as valid the correlation between the sequence of instantaneous vectors calculated by distant leads and the sequence of auricular and ventricular activation. If this correlation is not taken into consideration, the vectorial analysis can give us a good orientation for reaching the clinico-electrocardiographic diagnosis, but from the physical point of view the foundation is not correct.

Third question: Can the leads that are used for the study of the equivalent vector be considered as well-known lines or planes of projection?

The field that surrounds the heart is not homogeneous nor infinite or isotropic. The distribution of potential is irregular and the current density vector refracts at those surfaces which separate two portions of the medium with different conductivity.

If the irregularities of the conducting medium are not corrected, the lines and planes of projection used in electrocardiographic and vectorcardiographic studies are really unknown. The Einthoven triangle as well as the Burger triangle are idealized schematics that approximate the real conditions of the subjects studied.

Several investigators have studied very carefully the conducting medium that surrounds the heart, and they have given different solutions for eliminating the irregularities of such a medium. In future papers we will study the main laws and characteristics of the volume conductors; in the meantime, we summarize three of the best methods proposed to eliminate the inhomogeneities of the conducting medium.

A. *Central terminal of Bayley:* Bayley[9] modified the central terminal of Wilson with different resistances in each one of the wires in order to obtain a potential in the terminal equal to that of the mid-point of the single dipole, a potential which is considered zero for the field of the heart. This new central terminal could be defined with the following formula:

$$\text{R.R.A.} = \text{R.L.A.} = 2.6\ \text{R.L.L.}$$

where R denotes resistance in the wire connecting the right arm (R.A.), the left arm (L.A.), and the left leg (L.L.).

B. *Frank's method for vectorcardiographic registration:* In Frank's method[11] 7 electrodes are used, 5 of which are placed at the transverse level of the ventricles (fifth intercostal space); the other 2 electrodes are placed one on the left leg and one on the back of the neck. In this paper it is not possible to analyze the three components Px, Py, Pz, and the electrical circuits of this method. We only list the advantages of the system as given by the author: (1) The method has been derived from theoretical and experimental studies. (2) It is accurate to ±15 per cent. (3) The torso shape is corrected. (4) The proximity of the left arm is avoided. (5) The method shows insensitivity to individual variability in location of the ventricles. (6) Muscle tremor and electrical interference are markedly reduced.

C. *Rijlant's method for vectorcardiographic registration:* Rijlant[12] uses a bidimentional or tridimentional resistor network which is connected directly with the natural diffuse conducting medium through a great number of electrodes distributed regularly at the boundary of the conducting medium. The characteristics of the network are the same from any one of the electrodes considered as the beginning of the circuit. The network is formed by a symmetrical circuit of elements with resistors of 5,000 ohms plus or minus 1 per cent. The circuit ends at one terminal point opposite to the recording electrodes. From this terminal point all the elements of the circuit show the same characteristics.

According to the author the values obtained in the interior of the circuit permit a true representation of the vectorcardiogram even in cases of marked asymmetry of the conducting medium.

The method has been used to obtain the horizontal vectorcardiogram in the human being. Twelve electrodes are placed around the thorax at the level of the heart. The location of the electrodes is unimportant, because the vectorcardiogram so obtained is always of the same size, morphology, and rotation. The same occurs in the other two planes. Therefore, a true spatial vectorcardiogram is recorded with this circuit.

Only approximate solutions are obtained with all these ingenious methods. Nevertheless, these are of great help in the vectorial or electrocardiographic studies.

2. *The Unipolar Morphologies.*—It is principally through the morphologies of the waves that the electrocardiologist is able to interpret the tracings. However, he must fully comprehend the meaning of these morphologies as well as using them for interpretation. In order to enable the electrocardiologist to attain such comprehension, we present three discussions that we consider as fundamental in this respect.

A. *Correlation between the unipolar morphologies and the instantaneous vectors representing the electrical forces of the heart:* Most of the unipolar morphologies can be explained satisfactorily by the main instantaneous vectors described in relation to the sequence of auricular and ventricular activation in normal as well as in pathologic cases. This statement signifies that through the unipolar morphologies we can get a very good idea of the sequence of the activation process. We consider this knowledge to be important, and it has been reached by direct investigation of auricular and ventricular depolarization in the dog's heart. We know that some extrapolation is being made when the experimental work performed on animals is applied to the human heart. However, we believe that this extrapolation is justified because of the following facts: (1) The intracavitary, epicardial, and thoracic leads are very similar in both species. (2) The anatomic findings of the bundle of His, the branches of the same bundle, and the main ramifications of these branches are strikingly similar in both hearts. (3) The electrocardiographic diagnoses proved by postmortem studies also justify the above-mentioned extrapolation.

Recent investigations[13-15] proved that the unipolar morphologies obtained at the epicardial surface of the human heart are very similar to those of the dog's heart.

The correlation between the instantaneous vectors and the unipolar morphologies will be greater when the registering electrodes are placed distant from the heart. Obviously, there is a perfect correlation when the electrical axis is determined by the unipolar leads or by the distant bipolar leads obtained with the same electrodes used for the unipolar leads. In these cases there is a perfect correlation between unipolar lead, bipolar lead, instantaneous vectors, and activation process.

The results are not so good when the exploring electrodes for the unipolar leads are placed closer to the heart and predominant positive deflections can be

found on the negative side of the field due to the equivalent dipole; according to the Stratton theorem[13] this means that in the series of spheric harmonics not only the first two terms are important but the third term as well, which corresponds to the potential given by a quadrupole, and, perhaps, the fourth term, which corresponds to an octupole, and maybe some subsequent terms.

If we speak in terms of solid angle when portions near the heart are explored, the distances between the different heart dipoles and the exploring electrode cannot be considered as equal nor can the vectorial summation be performed. In electrocardiographic interpretation we consider in such cases the "local effects," emphasizing that the proximity of the heart prevents us from speaking of equivalent vector or dipole.

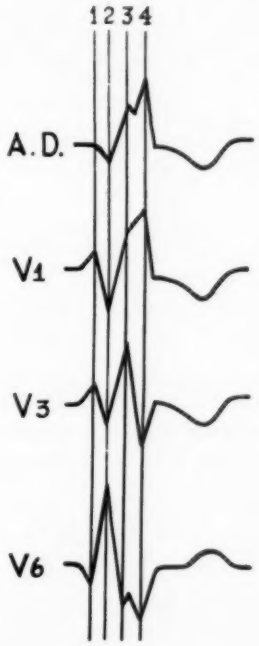

Fig. 1.—Vector 1: Activation at the middle third of the left septal mass. Vector 2: Activation of the free left ventricular wall. Vector 3: "Jumping" of the activation wave in the septal barrier and activation of some portions of the low right septal mass. Vector 4: Activation of the free right ventricular wall and high right septal masses.

B. *Correlation between the unipolar morphologies and the sequence of ventricular activation:* In this respect important scientific advances have been made, and in the unipolar morphologies we recognize fine details of ventricular activation. An example is that of right bundle branch block morphologies shown in Fig. 1; in septal activation three different phases can be distinguished: Vectors 1, 3, and 4. Vector 1 corresponds to normal activation of the left septal mass, which is not modified by the block in the right branch. Vector 3 corresponds to the "jumping" of the activation wave from the left to the right septal mass.[13] In this "jumping" process the activation rate diminishes importantly. The depolarization of the upper right septal mass plus the activation of the free right ventricular wall explain Vector 4.

Some investigators have denied the existence of a "barrier" separating both septal masses, and have denied a reduction in the speed of the activation wave in the intraseptal mass*; however, when they try to explain the curves of bundle branch block, they are obliged to draw the boundary and to give different speeds to the activation wave within the septum.

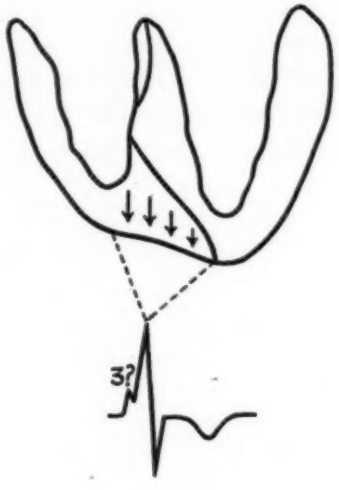

Fig. 2.

The four main ventricular activations in right bundle branch block are explained satisfactorily by the instantaneous vectors or equivalent dipoles (Fig. 1). There are, however, some morphologies in right bundle branch block which cannot be explained by the four vectors mentioned; they are frequently recorded in Leads V_3, V_4, and V_5 (Fig. 2). It is necessary to invoke "local effects" in the low portions of the right septal mass (Fig. 2) in order to explain such morphologies, which are very common findings in congenital heart diseases with marked right ventricular hypertrophy. Summarizing this paragraph, we state that most of the unipolar morphologies are explained satisfactorily by the sequence of ventricular activation, and that there is, generally, a good correlation between the instantaneous vectors and such morphologies. In a few cases "local effects" must be taken into consideration in order to completely understand the tracings.

C. *Correlation between the unipolar morphologies and the variations in potential at the auricular and ventricular epicardial surfaces:* Wilson and co-worker[7] were the first to point out the great similarity between the thoracic curves and those recorded at the epicardial surfaces of both ventricles. After several experiments Wilson showed that the variations in potential of the trabecular zone of the right ventricle are registered in Leads V_1 and V_2; the variations in potential of the interventricular septum are obtained in Leads V_3 and V_4, and Leads V_5 and V_6 correspond to the variations in potential of the free left ventricular wall.

*Very recently, Hibino and Mizuno confirmed this delay in septal conduction across the boundary in cases of bundle branch block and ventricular extrasystoles.[17]

Wilson's statements, although expressed in a correct mathematical sense, have been misunderstood by a great many investigators. It has been erroneously stated that Wilson and his school explained the curves recorded at the precordium by the activation of isolated zones of the heart; what has really happened is that the critics have confused the physical term *variations in potential* with the physiologic term *activation*. We believe that it is convenient to clarify all these concepts in order to propagate Wilson's ideas.

When we speak of activation we admit that at the boundary between activated and unactivated tissue, positive and negative charges appear which are the origin of the electrical field of the heart. When we speak of variations in potential we do not refer to those charges that give origin to the electrical field of the heart but to the variations of potential in the medium that surrounds those charges. It is convenient to remember that any portion of the heart belongs to the conducting medium before and after, but not during, activation.

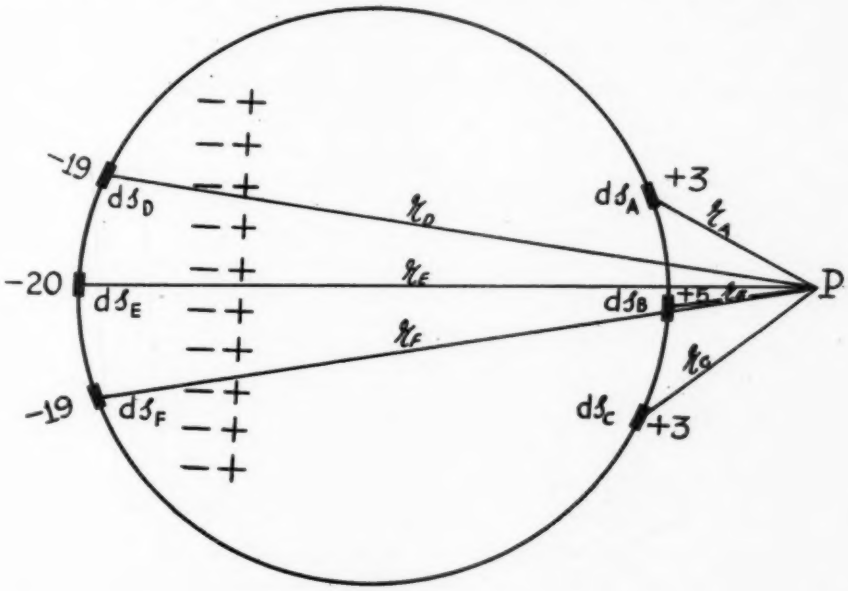

Fig. 3.

In the unipolar morphologies all that portion of QRS inscribed before the intrinsic deflection (preintrinsic) and those inscribed after (postintrinsic) correspond to the variations in potential of the conducting medium, even in those cases in which the tracings are recorded directly in the heart. The explored site (unipolar lead) is the partial or total source of the electrical field of the heart only during the inscription of some segment (variable) cf the intrinsic deflection. For example, during normal septal activation the free left ventricular wall forms a part of the conducting medium, and for this wall the term "variations in potential" must be used. If the exploring electrode of a unipolar lead is placed at the epicardial surface of the free left ventricular wall, variations in potential are recorded until the subepicardial muscle in contact with the electrode becomes activated. At the moment of activation of this subepicardial muscle fiber,

positive and negative charges appear as the origin of the electrical field of the heart. When the activation wave leaves the exploring electrode, variations in potential are again registered, because of the depolarization of the muscular portions near the base of the heart.

Wilson and his co-workers have studied this problem mathematically, applying the Poisson integral to the heart.[16] To facilitate an understanding of this integration we present some simplified examples.

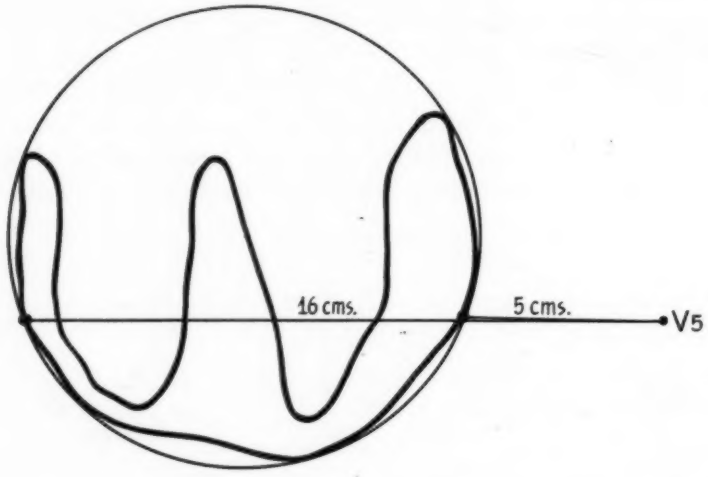

Fig. 4.

Suppose many electrical charges enclosed by one sphere. The electrical potential at any point of the sphere surface is due to the electrical charges within it. Let us imagine one sphere such as that represented in Fig. 3. In this illustration we have represented 6 small areas (dS) at the surface of the sphere, and the adjacent numbers correspond to the potential cause by the charges within the sphere. The potential at any point P outside the sphere (Fig. 3) can be calculated by two different methods: (1) in relation to the charges situated within the sphere—this is the analysis by the solid-angle or equivalence theorem (see above); (2) in relation to the distribution of potential at the surface of the sphere, using Poisson's integral. The final result will be identical.

By Poisson's integral it is demonstrated that the potential of each small area dS of the surface of the sphere determines a potential at P which is inversely proportional to the cube of the distance separating both sites (P and dS). In the case of Fig. 3, the voltage at P is obtained approximately by the following formula:

$$V_P = \left(\frac{V_A}{r_A^3}\,dS_A + \frac{V_B}{r_A^3}\,dS_B + \frac{V_C}{r_C^3}\,dS_C + \frac{V_D}{r_D^3}\,dS_D + \frac{V_E}{r_E^3}\,dS_E + \frac{V_F}{r_F^3}\,dS_F\right)K$$

and other terms of the small areas not represented in Fig. 3, where V_A is the potential of Point A, and V_B is the potential of Point B, and so on.

It is evident that the influence of the potential at the small areas A, B, and C on the potential of P is greater than the influence of the areas D, E, and F,

since the distances r_A, r_B, and r_C are smaller than r_D, r_E, and r_F. The potential at P is positive in this example even though the absolute values of the negative potential in D, E, F and adjacent regions are greater than the absolute values of positive potential in A, B, C and adjacent regions; in other words, the potential at P is due mainly to the potentials of A, B, C and of the adjacent regions. If we take into consideration all the elemental areas at the surface of the sphere instead of the 6 represented in Fig. 3, the potential at P is caused mainly by the surface potentials of the sphere near P. We must remember, however, that the variations in potential at the surface depend on the distribution of charges within the sphere. This procedure corresponds to a surface integration of the potential produced by the charges instead of calculating it directly with relation to the same charges. The validity of this explanation is proved by the analysis of Poisson's integral, an analysis which Wilson applied to the heart.

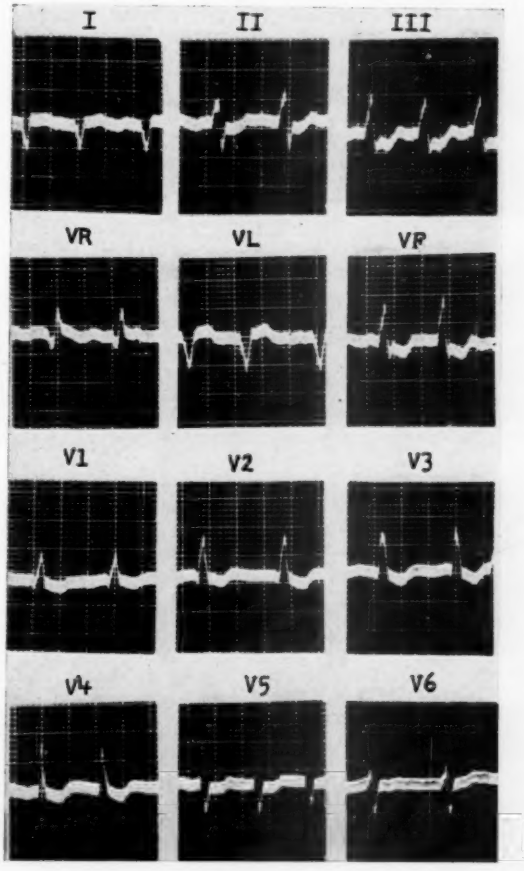

Fig. 5.

In Fig. 4 the two ventricles are represented schematically within an adequate sphere of the smallest possible radius. In the same figure we are supposing that Lead V_5 is facing the free left ventricular wall. Radiographic studies show that the distance between the precordial site where Lead V_5 is obtained and the

nearest epicardial surface of the left ventricle is about 5 cm., while the distance from Lead V_5 to the diametrically opposed points at the epicardial surface of the right ventricle is about 16 cm. The cube of these distances gives in the previously mentioned formula a denominator of 125 for the nearest sites of the left ventricle, while the denominator for the opposite sites of the right ventricle is 4,096. Dividing 4,096 by 125, the coefficient is 32.8, which means that the influence of the left ventricular surface on Lead V_5 is 33 times greater than the influence of the opposite similar surface in the free right ventricular wall. If the variations in potential at different epicardial regions of the free left ventricular wall are similar, as is suggested by the sequence of ventricular activation, what a correct statement was that given us by Wilson when he said that Leads V_5 and V_6 mainly register the variations in potential* of the free left ventricular wall!

IMPORTANCE OF THE UNIPOLAR LEADS IN THE INTERPRETATION OF THE ELECTROCARDIOGRAM

We believe that the best way to prove the importance of the unipolar leads is by presenting some examples in which these leads reflect the variations in potential of some portions of the heart; using this method we find that the spatial position of the auricles and ventricles, as well as their main anatomic changes, can be determined. The value of the unipolar morphologies only will be discussed in the following tracings. Other electrocardiographic signs will not be taken into account.

First Tracing (*Fig. 5*).—This electrocardiogram was recorded on a 71-year-old woman. From Lead V_1 through V_4 the ventricular morphology is of the qR type, with negative T wave. The R wave is slurred and the tracing suggests incomplete right bundle branch block. The qR morphology is the one that we have described[13] as corresponding to variations in potential of the right atrium when right bundle branch block is present. Because these morphologies are recorded from Lead V_1 through V_4, the tracing suggests a huge right atrium. In Lead V_5 the complex is of the qRS type, which may correspond to high right ventricular portions; although this pattern is also recorded in the left ventricle, it is difficult to admit that the left ventricle could be close to the right atrium. In Lead V_6 the complex is of the RS type, with an initial slurring in the upstroke of the R wave and with delayed intrinsicoid deflection (0.04 sec.), suggesting that we are exploring the low right septal mass. The presence of right bundle branch block must not be forgotten. The tracing, therefore, suggests that the right atrium and ventricle occupy all of the anterior aspect of the heart.

The Q waves present from Lead V_1 through V_4 could correspond to an anteroseptal infarction; but the reduction in voltage of Q from Lead V_2 to V_3, and the septal morphology present until Lead V_6 make this possibility quite improbable. In summary, the unipolar morphologies suggested a huge right atrium,

*It must be remembered that the variations in potential of the left ventricular surface depend on the distribution of charges in the entire heart and not only on the charges near that surface, as has been erroneously interpreted.

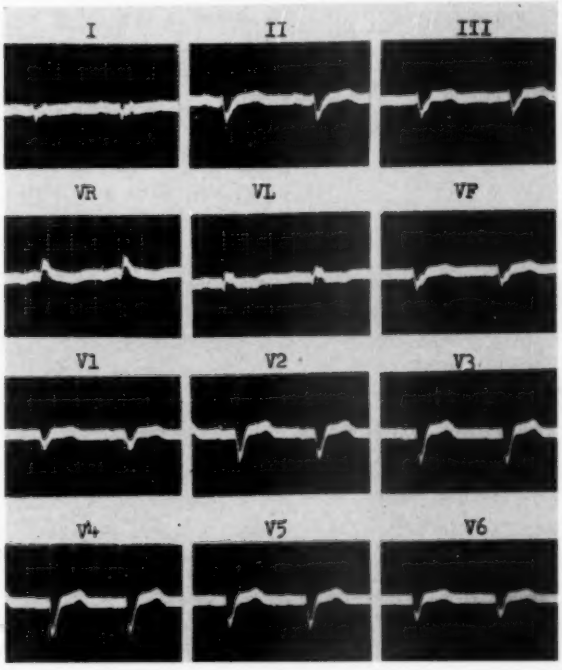

Fig. 6.

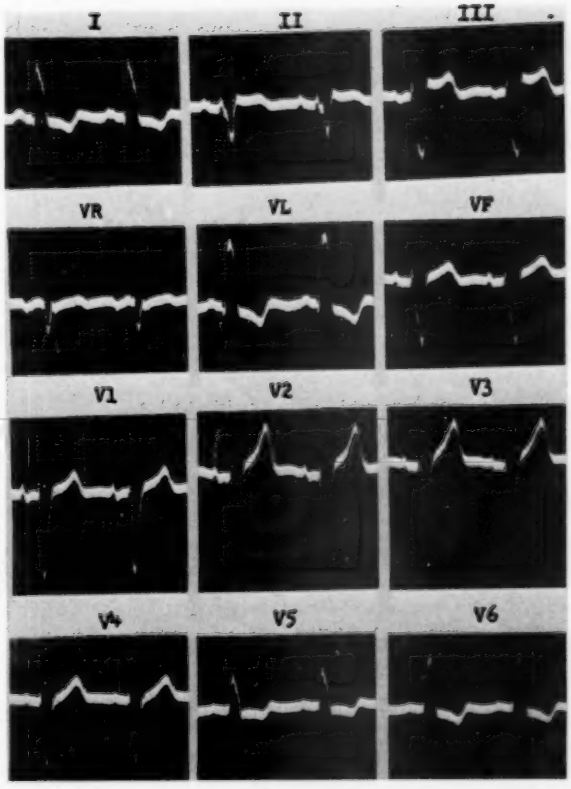

Fig. 7.

a right ventricular hypertrophy, and an interventricular septum spatially oriented parallel to the frontal plane. From the clinical point of view, taking into account the age of the patient, two main possibilities were considered*: chronic cor pulmonale and atrial septal defect. Inasmuch as auricular fibrillation was the basic rhythm, two other clinical diagnoses were postulated: myocardial sclerosis secondary to coronary atherosclerosis and an old rheumatic disease. (The incidence of rheumatic disease is high in Mexico City.)

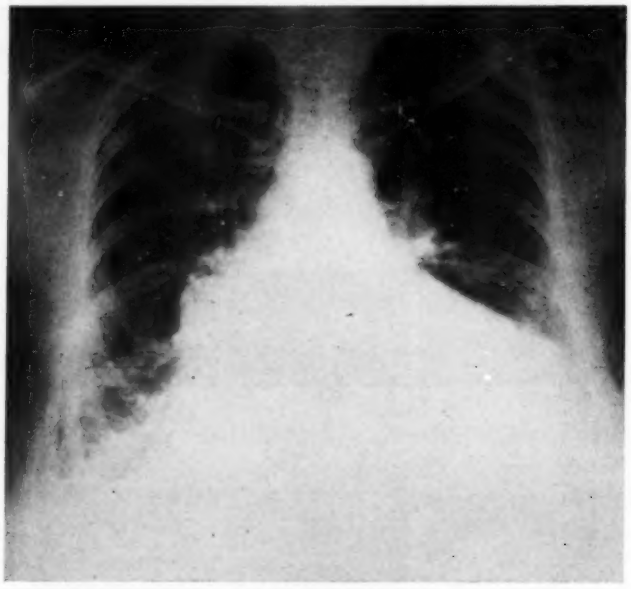

Fig. 8.

The postmortem study proved many of the aforementioned possibilities: (1) marked right atrial enlargement (no myocardial infarction being proved); (2) marked right ventricular enlargement; (3) the interventricular septum parallel to the frontal plane and all of the anterior aspect of the heart occupied by the right cavities; (4) atrial septal defect; (5) rheumatic mitral stenosis (Lutembacher's syndrome); (6) chronic cor pulmonale.

This example illustrates the usefulness of the unipolar morphologies in the recognition of the position and enlargement of the heart's cavities. We do not believe that the diagnosis proposed could be reached by vectorial study, inasmuch as only right ventricular hypertrophy was suggested.

Second and Third Tracings (Figs. 6 and 7).—These tracings are from a 52-year-old woman. The first electrocardiogram (Fig. 6) shows a qR complex in Lead V_L, with delayed intrinsicoid deflection and negative T wave very suggestive of complete left bundle branch block. A member of our Department thought about the possibility of right bundle branch block because of the mor-

*In the Department of Electrocardiography of the National Institute of Cardiology, in Mexico City, this procedure is followed: The electrocardiogram is interpreted and a diagnosis is suggested through the tracing; after this, it is compared with the clinical record.

phology in Lead V_R. But if we accept the latter possibility, the result is that the electrocardiogram is not understood. We will discuss this subject in the following paragraph.

In all the precordial leads, QS complexes with negative T waves are recorded, corresponding to the variations in potential of the right ventricle in the presence of left bundle branch block. This means that the right ventricle occupies, as in the previous example, all of the anterior aspect of the heart. If instead of admitting left bundle branch block we consider right bundle branch block, we would be forced to admit also that the left ventricle occupies all of the anterior aspect of the heart, which is practically impossible; therefore the possibility of right bundle branch block can be ruled out. The variations in potential of the right ventricle are recorded in all the precordial leads in very marked horizontal hearts with counterclockwise rotation around the longitudinal axis, and in which an important portion of the free left ventricular wall faces Lead V_L (Fig. 6).

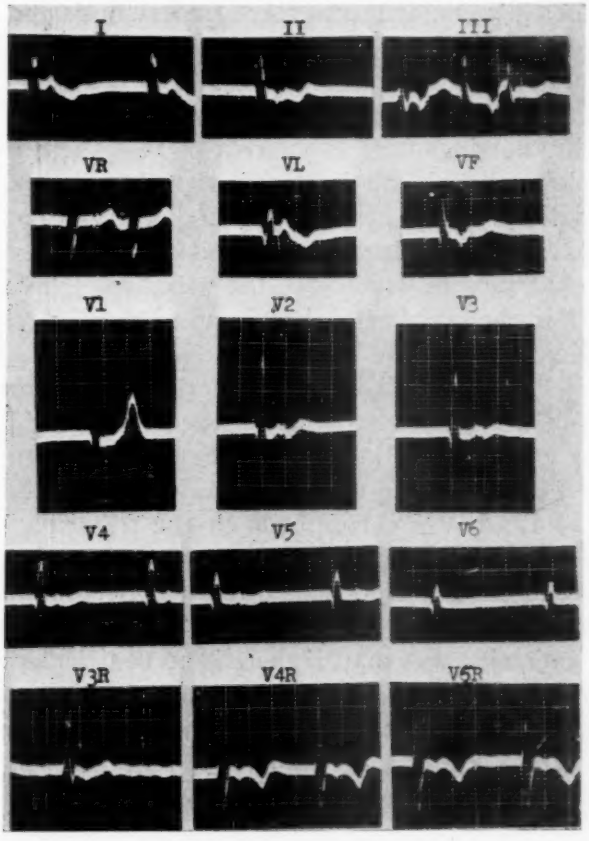

Fig. 9.

The possibility of an important right ventricular hypertrophy is very limited in the presence of left bundle branch block.

A second tracing (Fig. 7) recorded a few days later shows important changes. The variations in potential of the free left ventricular wall in the presence of

left bundle branch block were recognized in Leads V_5 and V_6. In addition, the horizontal position of the heart diminished, in view of the fact that the right ventricular morphology was recognized only from Lead V_1 through V_4 and not from Lead V_1 through V_6 as shown in the first tracing taken on this same patient. Such an important change in the position of the heart suggested an extracardiac cause which pushed the heart upward, making us consider ascites or other abdominal pathology. We reviewed the clinical history and found that the patient was in marked heart failure, and that an abdominal puncture had been performed in the interval between the two tracings. The puncture reduced considerably the ascites—8 liters of fluid were removed. A radiographic study made after the puncture still showed a marked horizontal heart (Fig. 8).

This case explains the unipolar morphologies in the presence of left bundle branch block and in accordance with the position of the heart.

Fourth Tracing (*Fig. 9*).—This tracing was recorded on a 9-year-old girl. In this case the vectorial analysis did not give the solution, but a careful study of the unipolar morphologies enabled us to reach the diagnosis and "to understand" the tracing.

There is infranodal rhythm with positive P in Lead I and negative P in Leads II, III, and aV_F. The ventricular complexes are of the qR type from Lead V_1 through V_6, with slurrings near the vertex of R. These morphologies may correspond to the left ventricle, or, if there is right bundle branch block, to the right atrium (variations in potential). The unipolar morphology in Lead V_R gives us the solution: the ventricular complex is of the RS type, with slurred S, a pattern very probably corresponding to the variations in potential of the free left ventricular wall in the presence of right bundle branch block; in other words, this morphology indicates that the left ventricle is right sided.

The tracing is "understood" if we admit these two diagnoses: (1) right bundle branch block and (2) transposition of the ventricles. With this in mind we can explain the morphologies in the different leads: the qR complexes from Lead V_1 through V_6 correspond to the variations in potential of the right atrium. The morphology in Lead V_{3R} corresponds to the free right ventricular wall, while the morphologies in Leads V_{4R} and V_{6R} are similar to those described by us as corresponding to the lower portions of the right septal mass. These diagnoses were objected to by clinicians and radiologists of our Institute. Our attitude toward their objection was that, if there is no ventricular transposition, we simply do not understand the tracing; but the angiocardiographic study proved our own diagnosis inasmuch as ventricular transposition was present in a patient with common trunk.

SUMMARY

The physical basis required to interpret the unipolar morphologies as corresponding to the variations in potential of some portions of the heart are presented (Poisson's integral). Several examples of the utility of these electrocardiographic analyses are discussed. We think that this new form of electrocardiographic interpretation gives a wider range of diagnoses than has been obtained so far through vectorial analysis.

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Clinical Value of Burger's Concept as Applied in Frank's Lead System

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The concept of Burger and van Milaan[1] on the lead vector and the heart vector has provided a powerful tool for clarifying the relationship between the electrical field of the inhomogeneous human body with its irregular boundaries and the heart with its eccentric position. Applying this concept, Burger and van Milaan,[1] Wilson, Bryant and Johnston,[2] Frank,[3,4] and other authors[5,6,7] reported the results of actual experimental determinations on models, torsos, or, indirectly, human bodies. These experiments, however, were performed on or in relation to a few individuals. For instance, Frank[3] modeled his homogeneous torsos from a male and a female, the values obtained from the male torso being verified in a later report[8] to fit the original male person. It has remained undetermined whether these values are or are not applicable to many other normal persons and cardiac patients. Recently, Frank[9] devised a lead system of vectorcardiography on the basis of his experimental results. Employing this system, it will be possible to investigate whether Frank's image surface, originated from a few individuals, is applicable to the majority. This is because a comparison between vectorcardiograms and electrocardiograms will decide the validity of the experimental data mentioned above, since in the concept of the lead vector as well as in the conventional concept it is theoretically predicted that patterns derived by the projection of vector loops into a lead vector should coincide with the actual electrocardiogram of the corresponding lead, insofar as the contour is concerned. This is the first purpose of this research, and its result should give an answer, in a sense, to what extent Burger's concept, being here concreted into Frank's data, is useful for clinical purpose.

Furthermore, from the vectorcardiographic point of view, such a comparison will decide the clinical value of Frank's lead system of vectorcardiography itself. Although matching with electrocardiograms is not a unique criterion for deciding whether one lead system of vectorcardiography is superior to another, it is strongly desired by some, from the clinical point of view. To determine whether this system satisfies such a desire is the second purpose of this study.

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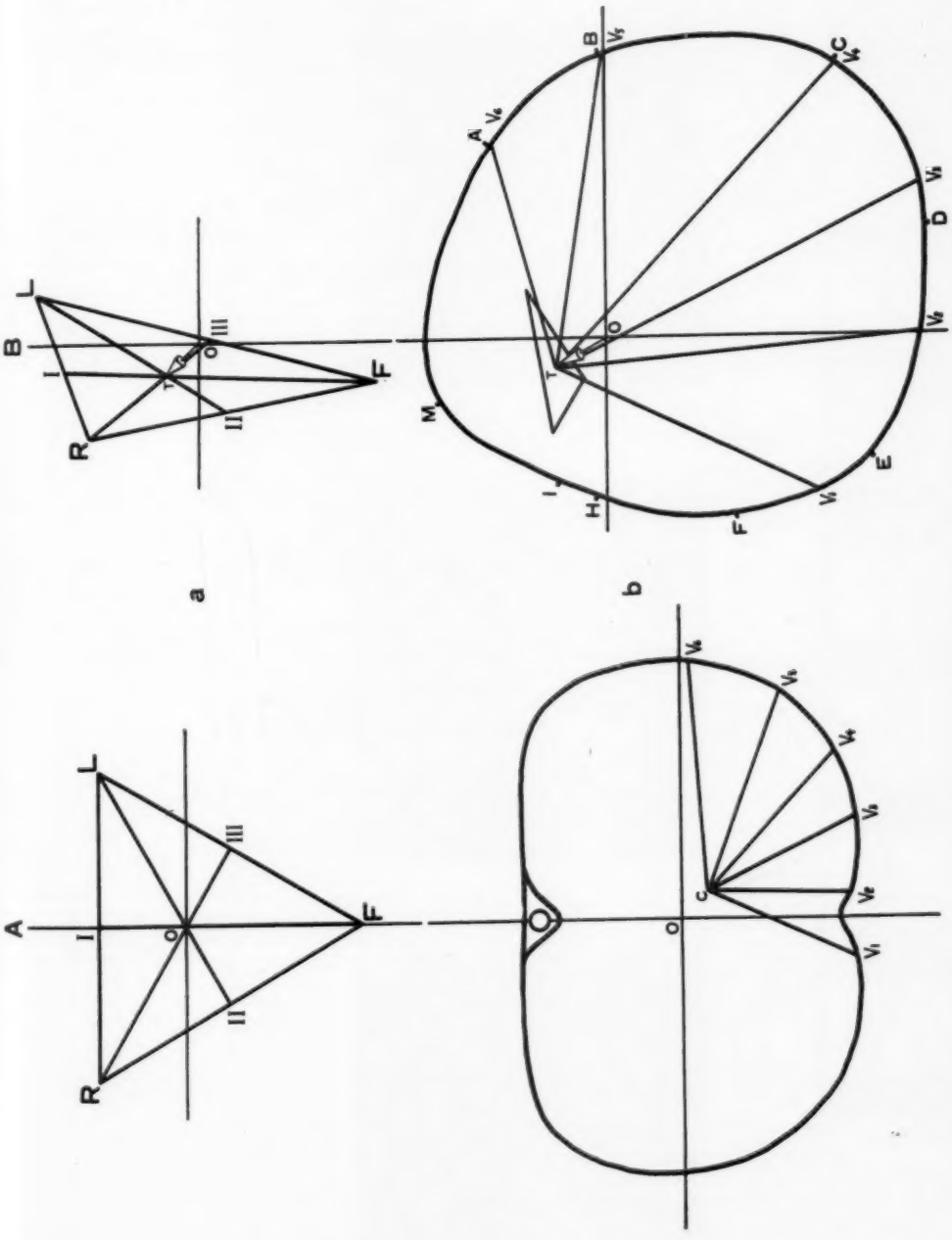

Fig. 1.—The conventional lead axes (*A*) and the lead vectors by Frank, modified slightly (*B*). Vector loops by Burch's and Grishman's methods were projected into *A* and those by Frank's method into *B*.

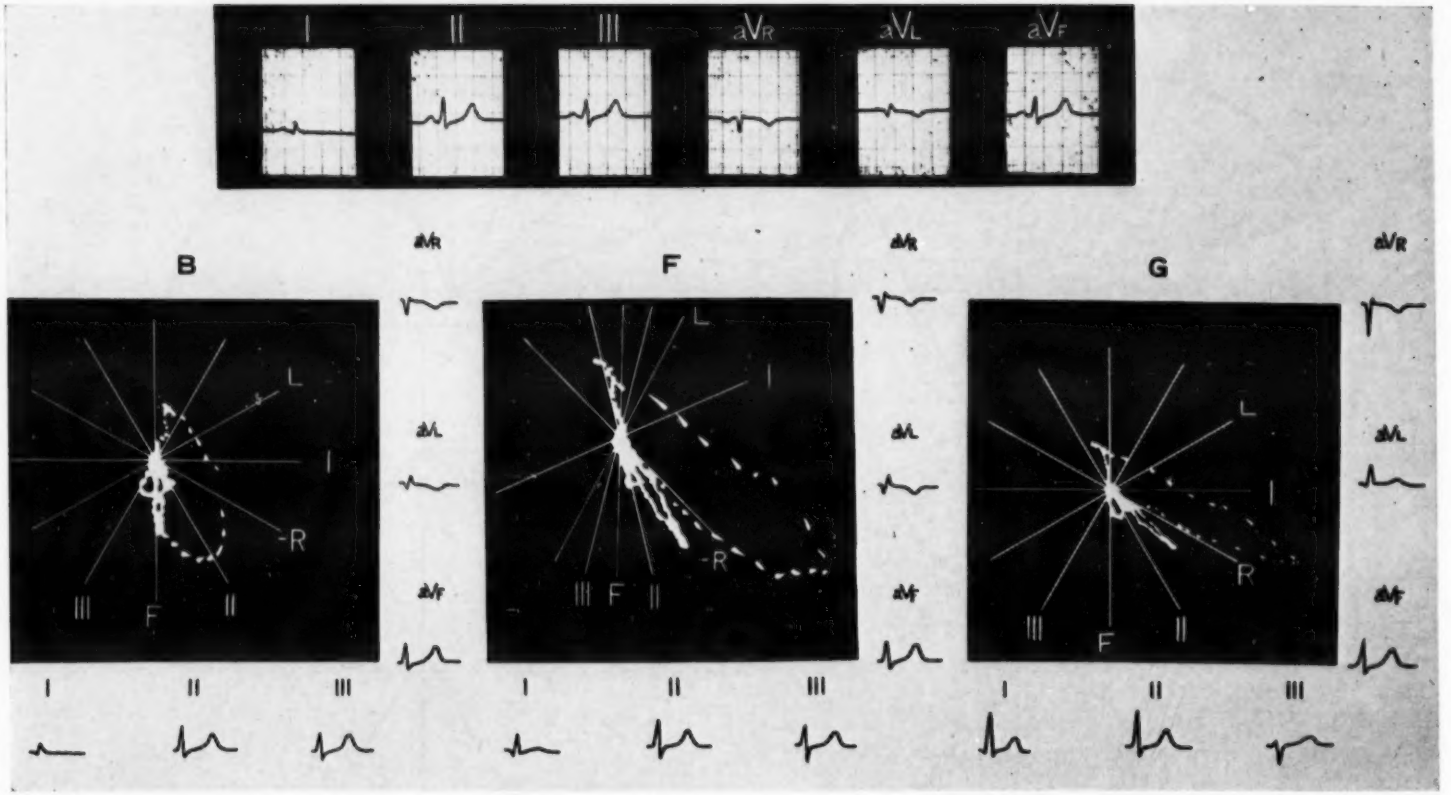

Fig. 2.—An example of comparison between derived patterns and actual electrocardiograms in the frontal plane. Patterns derived from each vector by Burch's (*B*), Frank's (*F*), and Grishman's (*G*) methods are drawn on the lower and right sides of each picture. Compared with the actual electrocardiogram, which is shown at the top of the figure, the derived R and T of Lead I in *G* are too large; in regard to Lead I the counts were 1 point for QRS and 1 point for T not matching. In *G* the derived QRS of Lead III is of the rS type in contrast with the Rs type of the actual one, counted as 2 points not matching; and in Lead aV_L, the derived q is too small, R is too large, and T is upright in contrast with the inverted T in the actual aV_L, being counted as 2 points for QRS and 2 points for T not matching. The derived patterns in *B* and *F* show good correspondence with the actual ones. Vector loops were interrupted at 500 cycles per second by intensity modulation. Segments were tapered, the pointed end indicating direction of movements of the loops.

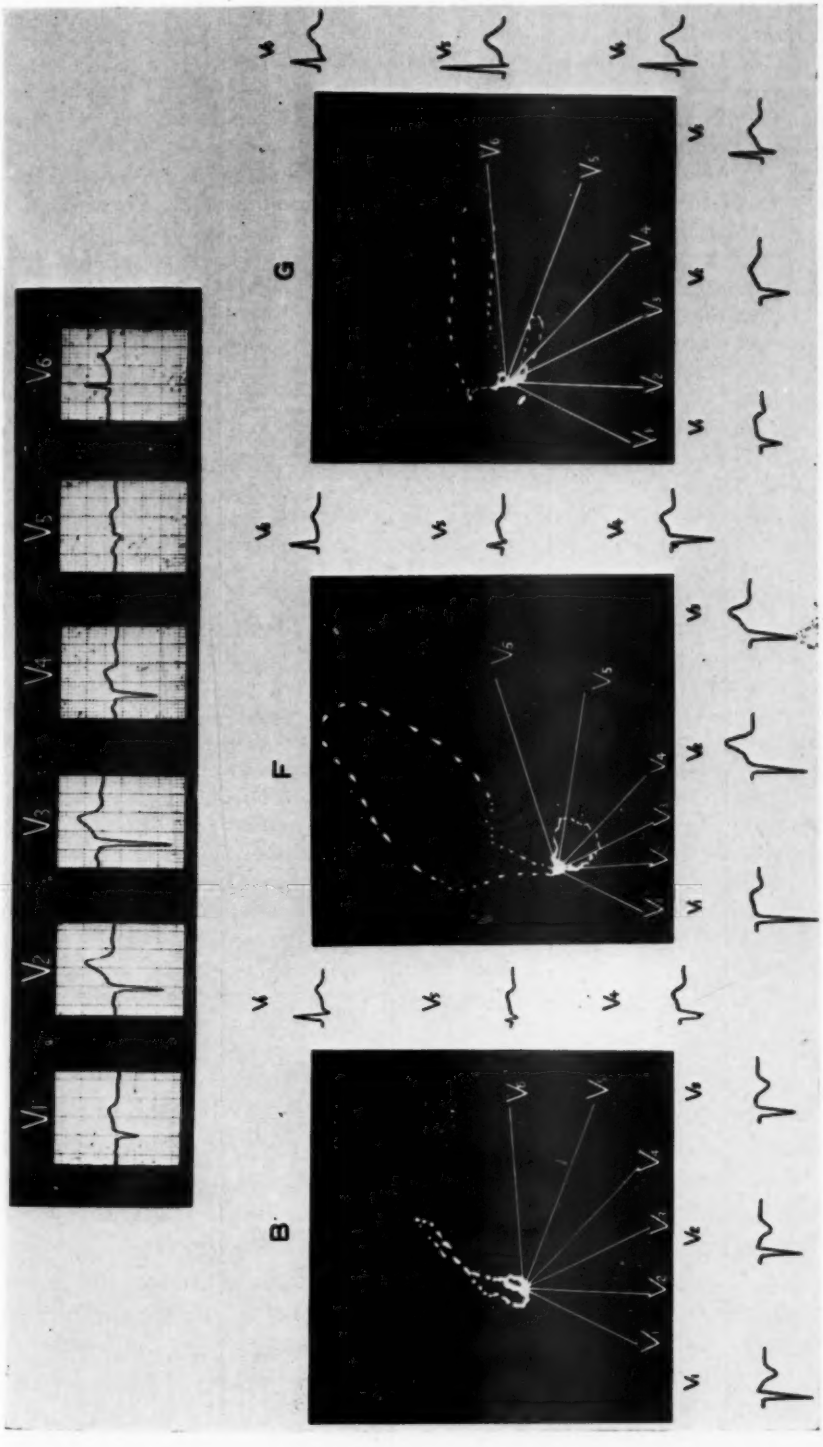

Fig. 3.—Comparison between derived patterns and actual electrocardiograms in the horizontal plane in the same case as that of Fig. 2. Arrangement of pictures and methods is the same as in Fig. 2. The differences between derived patterns and the actual electrocardiograms, with the count of points of discrepancy given in parentheses, are: in *B*, the presence of a minute r in V_1 (1), the presence of r in V_5 (1), the presence of s in V_6 (1), the inversion of T in V_1 (2), V_2 (2), and V_3 (2); in *F*, the presence of qr in V_4 (1), and the presence of r in V_5 (1); in *G*, the Rs type in V_3 (2), V_4 (2), and V_5 (2), the presence of s in V_6 (1), and a maximal T in V_5 (1).

TABLE I. EVALUATION AS TO WHETHER FRANK'S VECTOR LOOPS AND LEAD VECTORS ARE APPLICABLE TO THE MAJORITY OR NOT BY COUNTING POINTS OF DISCREPANCY

		I		II		III		aV_R		aV_L		aV_F		LIMB LEADS (TOTAL)	V_1		V_2		V_3		V_4		V_5		V_6		CHEST LEADS (TOTAL)	TOTAL
		QRS	T	QRS	T	QRS	T	QRS	T	QRS	T	QRS	T		QRS	T	QRS	T	QRS	T	QRS	T	QRS	T	QRS	T		
A. Normal Adults (30)	Total Counts	120	60	120	60	120	60	120	60	120	60	120	60	1,080	120	60	120	60	120	60	120	60	120	60	120	60	1,080	2,160
	F	5	0	3	0	10	2	3	0	15	21	5	0	64	3	6	9	0	9	0	7	0	12	0	8	2	56	120
	B	6	0	3	1	13	4	7	0	6	6	5	0	51	23	26	27	21	29	2	18	1	19	2	20	1	189	240
	G	24	0	7	0	30	12	14	0	40	15	9	0	151	14	25	29	7	36	0	20	1	12	2	12	1	159	310
B. Cardiac Patients (126)	Total Counts	504	252	504	252	504	252	504	252	504	252	504	252	4,536	504	252	504	252	504	252	504	252	504	252	504	252	4,536	9,072
	F	41	7	22	7	45	28	25	6	45	45	36	15	322	14	23	13	29	19	11	29	9	39	17	33	21	257	579
	B	39	8	28	10	42	30	29	11	36	21	36	23	313	32	69	36	75	54	30	55	20	63	26	55	30	545	858
	G	38	15	32	10	84	35	31	9	70	39	48	28	439	31	67	33	82	74	34	61	20	44	26	37	32	541	980
C. Total Cases (156)	Total Counts	624	312	624	312	624	312	624	312	624	312	624	312	5,616	624	312	624	312	624	312	624	312	624	312	624	312	5,616	11,232
	F	46	7	25	7	55	30	28	6	60	66	41	15	386*	17	29	22	29	28	11	36	9	51	17	41	23	313*	699*
	B	45	8	31	11	55	34	36	11	42	27	41	23	364	55	95	63	96	83	32	73	21	82	28	75	31	734	1,098
	G	62	15	39	10	114	47	45	9	110	54	57	28	590	45	92	62	89	110	34	81	21	56	28	49	33	700	1,290

*364:386 $\chi^2 = 0.69$, 386:590 $\chi^2 = 46.7$
364:313 $\chi^2 = 4.08$, 313:700 $\chi^2 = 162.3$
699:1098 $\chi^2 = 9.58$
$\chi^2_{1,\,0.05} = 3.841$, $\chi^2_{1,\,0.1} = 2.706$, $\chi^2_{1,\,0.3} = 1.074$

F: Frank's method. B: Burch's method. G: Grishman's method.

MATERIAL AND METHODS

The total material of 156 cases was comprised of 30 normal adults and 126 adult cardiac patients. Most of the normal subjects were healthy medical students. The others were outpatients of the Tokyo Medical and Dental University Hospital, who were proved by routine clinical examination to have no cardiac disease. The cardiac patients included persons with right and left ventricular hypertrophy, bundle branch block, subendocardial ischemia, and myocardial infarction according to electrocardiographic and vectorcardiographic diagnosis.

In each case vectorcardiograms were taken by three methods: by Frank's method[9]; by that originated by Wilson and developed by Burch[10] (designated as Burch's method in this paper); and by that of Duchosal as modified by Grishman[11] (designated as Grishman's method). The standard 12 leads of the electrocardiogram were also recorded. The latter two methods of vectorcardiography were adopted as representative of those based on the conventional concept in order to judge the degree of correspondence between the vectorcardiogram by Frank's method and the electrocardiogram, as compared to the correspondence between that by Burch's method and the electrocardiogram, and to the correspondence between that by Grishman's method and the electrocardiogram. In a slight departure from Burch's original idea, the horizontal plane, not the tilted superior plane of the equilateral tetrahedron, was considered to be obtained by combining Lead I and Lead V_B using Wilson's central terminal multiplied by the same coefficient as reported by Burch and associates.[10] These vectorcardiograms were projected into the corresponding lead vector or lead axis, and the patterns of ventricular complex thus obtained were compared with the actual electrocardiograms, that is, the frontal plane vectorcardiograms taken by Burch's and Grishman's methods were projected into the conventional hexaxial reference system derived from Einthoven's equilateral triangle (Fig. 1,*Aa*). Their horizontal plane vectorcardiograms were projected into one of the conventional lead axis systems of the precordial leads as shown in Fig. 1,*Ab*. Since the exact localization of the electrical center of the heart has not been determined as yet, such an arbitrary system may be admitted. For the same reason the level difference among the precordial lead axes was not considered for simplification. Vectorcardiograms taken by Frank's method were projected to the direction of the lead vector of the corresponding leads derived from the results published by Frank (Fig. 1,*B*). The exact localization of the precordial lead points on the image surface has not been described by Frank. Therefore, the derivation by Helm[12] from Frank's data was adopted. Frank reported two kinds of triangles for the frontal plane, namely, that obtained from the male torso and that from the female torso. Because of the minor difference between the two, and because of the statistical nature of this research, only the one from the male torso was adopted. The comparison of derived patterns with actual electrocardiograms was performed as accurately as possible, but only in regard to configuration, and the magnitude of each component was not measured.

RESULTS

Mentioning and comparing the number of cases in which the vectorcardiograms did not correspond completely with the electrocardiograms would be rather irrational, since a case in which the electrocardiogram is different from the vectorcardiogram in only a very minor point in any one lead and a case in which the electrocardiogram shows a marked difference from its vectorcardiogram in many leads would be counted equally as a single case. Therefore, the count was made as follows: When there was a difference between the pattern derived from the vectorcardiogram and the electrocardiogram in the chief deflection of either the QRS complex or the T wave (S-T segments were included here) in any one lead, such as when the main deflection was positive in one and negative in the other, a count of 2 points was made for the noncorrespondence. And when there was a minute difference between them in a lead, such as absence or presence of q or s in the QRS complex, or minor difference in the T wave, a count of 1 point

was made for noncorrespondence (Figs. 2 and 3). Four points were decided as the total count for the QRS in one lead of one case and 2 points for that of T. Therefore in one lead there were 6 points, and in one case with 12 leads there were 72 points. Of course, such counting is arbitrary, but it seems to be a much more rational means of expressing the actual state of comparison than is counting the number of cases.

The results of such counting of points of discrepancy between vectorcardiograms and electrocardiograms are listed in Table I, A for 30 normal adults, in Table I,B for 126 cardiac patients, and in Table I,C for the total 156 cases. The data in Table I,C indicate that in the total count of 11,232 points the patterns derived from vectorcardiograms by Frank's, Burch's, and Grishman's methods showed variance with actual electrocardiograms in 699, 1,098, and 1,290 points, respectively. This shows that, from the statistical point of view at the 5 per cent level, the vectorcardiograms which take into consideration the eccentricity of the heart in the body and the irregularity of the boundary of the human body, such as is done in Frank's determination, show significantly a superior coincidence with electrocardiograms as compared to those based on conventional simplified assumption. Looking at the details of Table I,C, we see that the points of discrepancy in the limb leads as between Frank's and Burch's methods show no statistically significant difference. As will be discussed later, the number of points of discrepancy in the limb lead with Burch's method indicates the extent of technical error in such a comparison, when theoretically such error should be zero. Therefore, this shows that the frontal plane vectorcardiograms by Frank's method correspond with the actual electrocardiograms to the ideal extent, or at least very well. The same is true of the horizontal plane vectorcardiograms by Frank's method. That the number of instances of discrepancy was slightly smaller in the precordial leads with Frank's method than was the number in the limb leads with Burch's method was probably due to the fact that Frank's vector loops were large and clear in details.

Although rather irrational, for the reason given previously, the number of cases which showed complete correspondence between vectorcardiograms and electrocardiograms is listed in Table II. This number is small and does not express well the actual state of good correspondence, but the conclusion from this table is also the same.

TABLE II. EVALUATION BY NUMBER OF CASES AS TO WHETHER FRANK'S VECTOR LOOPS AND LEAD VECTORS ARE OR ARE NOT APPLICABLE TO THE MAJORITY

METHOD	NUMBER OF CASES WHICH SHOWED COMPLETE CORRESPONDENCE WITH 6 LIMB LEADS	NUMBER OF CASES WHICH SHOWED COMPLETE CORRESPONDENCE WITH 6 CHEST LEADS	NUMBER OF CASES WHICH SHOWED CORRESPONDENCE WITH LESS THAN 6 POINTS OF DISCREPANCY IN TOTAL OF ALL LEADS
Frank's	27	37*	100
Burch's	26*	5	59†
Grishman's	9	6	33†

*$\chi^2 = 2.41$
†$\chi^2 = 10.42$

DISCUSSION

It does not seem ever to have been emphasized that the pattern obtained by projection into the conventional hexaxial reference system of frontal plane vectorcardiograms by Burch's method should theoretically conform completely with each of all the actual limb lead electrocardiograms. It is the same whether Einthoven's equilateral triangle model does or does not apply to the actual human body. The proof is given in the addendum. The points of discrepancy in this comparison in Table I,C were due mainly to the fact that the details of the vectorcardiograms taken routinely were sometimes obscure, especially in the vicinity of the isoelectric points. The situation is quite different with others. Except for frontal plane vectorcardiograms by Burch's method there is no reason to predict correspondence between vectorcardiograms and electrocardiograms unless the relation between the electrical motive force of the heart and the human body is as assumed by Einthoven and by the conventional thought in other planes by Burch's method and in all the planes by Grishman's method, or is such that Frank's data obtained from a few individuals apply to the majority in vectorcardiograms by Frank's method. Therefore, our results which show good correspondence in Frank's method support the latter view, that is, Frank's data apply roughly to the majority of adults regardless of whether they are normal persons or cardiac patients. Insofar as the frontal plane is concerned, this was proved by the present authors by different methods in another group of 275 persons, including infants and children, and was reported elsewhere.[13]

As for the second purpose of this study, Frank's lead system was shown to have stronger points in matching with electrocardiograms than did the other systems; the correspondence was as good as with Burch's method in the frontal plane and was superior to the other two in the horizontal plane. In addition, the size of the vector loops is large, and information about the details can be obtained with less amplification. But normal horizontal loops seemed to show more variation than those by Grishman's method. The normal horizontal QRS loop often extended so far posteriorly by Frank's method that differentiation of its configuration from that of left ventricular hypertrophy was sometimes difficult. Furthermore, because of the complexity of Frank's lead system, employing more electrodes than Burch's and Grishman's methods, the majority of investigators may still have a tendency to prefer one of the latter two.

SUMMARY

1. In each of 156 cases, including 30 normal adults and 126 cardiac patients, vectorcardiograms were taken by three methods, i.e., Frank's, Burch's, and Grishman's methods, and standard 12-lead electrocardiograms were recorded. Burch's and Grishman's vector loops were projected into the conventional lead axes and Frank's vector loops into the lead vectors, and the patterns of ventricular complex thus obtained were compared with actual corresponding electrocardiograms.

2. It was found that the patterns derived from Frank's vector loops showed a much better conformity to the actual electrocardiograms than did those from the vector loops by the other two methods.

3. This good conformity of Frank's vector loops in a number of cases shows that, even though Frank's image surface was obtained from a few individuals, it is applicable to the majority, both healthy persons and cardiac patients. It suggests also the clinical usefulness of Burger's concept.

4. Moreover, such conformity of Frank's vector loops increased the clinical value of his lead system of vectorcardiography.

5. It was pointed out that frontal vector loops by Burch's method should theoretically conform completely with limb lead electrocardiograms regardless of whether Einthoven's triangle does or does not apply to the actual human body. The excellent conformity was also actually verified. This fact gives a strong point, in a sense, to Burch's lead system of vectorcardiography, in so far as its frontal plane is concerned.

ADDENDUM

When the frontal plane vector loops by Burch's method are projected into the conventional hexaxial reference system originated from Einthoven's triangle, the derived patterns should theoretically conform completely with the corresponding limb lead electrocardiograms, regardless of whether or not Einthoven's triangle model holds true to the human body. The reason is proved quite simply with Lead II, as follows. Since with Burch's method, vector $\vec{E}$ is obtained on the screen of the cathode-ray oscilloscope by connecting the horizontal plates with Lead I of the electrocardiogram and its vertical plates with $\sqrt{3}\,V_F$,

$$\tan\alpha = \frac{\sqrt{3}\,V_F}{I}, \quad E\cos\alpha = I \tag{1}$$

where α is the angle between $\vec{E}$ and the horizontal axis. When this $\vec{E}$ is projected into each side of Einthoven's equilateral triangle, II′ thus derived, which corresponds to Lead II, is:

$$\begin{aligned} II' &= E\cos(60^\circ - \alpha) \\ &= E\cos\alpha \cdot \left(\tfrac{1}{2} + \frac{\sqrt{3}}{2}\tan\alpha\right) \end{aligned}$$

By replacing the right side with (1),

$$= \frac{I + 3\,V_F}{2} \tag{2}$$

On the other hand, the magnitude of Lead II of the electrocardiogram is obtained physically, regardless of whether or not Einthoven's equilateral triangle model is applicable to the human body, as follows:

$$I = V_L - V_R \tag{3}$$

$$II = V_F - V_R \tag{4}$$

$$V_R + V_L + V_F = 0 \tag{5}$$

The foregoing well-known equations were introduced on the basis of Einthoven's equilateral triangle theory in some textbooks, but these equations can be proved easily by employing the following relations which hold regardless of whether or not this triangle is applicable to the human body.

$$I = \varphi_L - \varphi_R,\ II = \varphi_F - \varphi_R,\ III = \varphi_F - \varphi_L,$$

$$V_R = \varphi_R - \frac{\varphi_R + \varphi_L + \varphi_F}{3},\ V_L = \varphi_L - \frac{\varphi_R + \varphi_L + \varphi_F}{3},\ V_F = \varphi_F - \frac{\varphi_R + \varphi_L + \varphi_F}{3}$$

where φ_R, φ_L, and φ_F are the potentials of the right arm, the left arm, and the left foot, respectively. Therefore,

$$(3) - (4) \quad I - II = V_L - V_F \tag{6}$$

$$(4) - (5) \quad II - V_L - V_F = V_F \tag{7}$$

$$(6) - (7) \quad II = \frac{I + 3V_F}{2} \tag{8}$$

By comparing (2) with (8): $II' = II$

The same proof can be performed similarly with other limb leads of the electrocardiogram.

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Case Reports

Persistent Left Superior Vena Cava Draining Into the Left Atrium, As an Isolated Anomaly

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Hitherto, the anomaly of persistent left superior vena cava draining into the left atrium has been regarded as rare. With the advent of cardiac catheterization as an indispensable diagnostic procedure, however, it is felt that far more cases will be diagnosed in the future.

The recognition of this anomaly is of importance for the following reasons: It may be an aggravating factor in an already cyanotic patient with a cardiac defect. If the heart condition is one that is not ordinarily suited for surgery, e.g., Eisenmenger's complex, tying off of such a persistent left superior vena cava emptying into the left atrium may relieve the cyanosis (Feindt and associates[4]). In patients in whom this is the only anomaly a corrective operation can bring about a complete cure, as described in the case reported herein.

A persistent left superior vena cava is probably found once in 350 autopsies (Keith and associates[8]). There are two types.

1. *Left Superior Vena Cava Draining Through the Coronary Sinus Into the Right Atrium.*—This is the anomaly most frequently found; it has no functional importance. It is usually discovered coincidentally at cardiac catheterization via the left arm, at thoracotomy, or during heart surgery.

Embryology: The anterior and posterior cardinal veins of the same side join to form a short main vessel, the ductus of Cuvier or cardinalis communis. They enter the dorsal part of the septum transversum and are joined there by the umbilical and vitelline veins to form the respective right and left horns of the sinus venosus. Caudal to the junction of the left innominate vein (an an-

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astomotic vessel between the left and right cardinal veins) and the left duct of Cuvier the anterior cardinal vein disappears and leaves as remnant a fibrous band, the ligament of Marshall. The caudal part remains patent and is known as Marshall's oblique vein. The left duct of Cuvier with the left horn of the sinus venosus together form the coronary sinus draining into the right atrium. Occasionally, it may drain into both atria.

The left superior vena cava will remain patent when: the left innominate vein does not develop or remains very small; or the anastomosis between the right and left superior venae cavae is such that the left innominate vein joins the right anterior cardinal vein at a higher level than the left, so that blood flows from right to left; or the superior sagittal sinus drains into the left side with increased flow on that side; or the pulmonary veins drain into the left superior vena cava; or the left anterior cardinal vein persists and that part between the left innominate vein and the ductus of Cuvier is the left superior vena cava.

Winter[11] found that the left superior vena cava draining through the coronary sinus into the right atrium was the type in 60 per cent of 174 cases collected from the world literature including his own.

The right superior vena cava is usually present but may be absent.

Partial pulmonary venous drainage into the left superior vena cava, before entering the coronary sinus, may also occur (Winter[11]).

The coronary sinus ends blindly and circulation is maintained via the innominate vein to the right superior vena cava.

2. *Persistent Left Superior Vena Cava Draining Into the Left Atrium.*—This anomaly is very rarely found, and is then associated with other congenital intracardiac abnormalities. Only once before, to our knowledge, has this been described as an isolated anomaly (Tuchman[10]).

Embryology: Very early venous connections are formed between the lung bud, anterior cardinal veins, or sinus venosus. The laevoatrial cardinal veins are examples of this (Edwards[3]). When there is an anastomosis between the pulmonary veins and superior vena cava, with the incorporation of the pulmonary veins into the left atrium, it may happen that the left superior vena cava is also incorporated so that it also drains into the left atrium. The anomaly may be associated with other cardiovascular defects. Winter collected some 14 cases. Some of these were described by the following authors: Diaz and associates,[2] Feindt and associates,[4] Gasul,[6] Friedlich and associates,[5] Peel and associates.[9] Other cases were reported by Campbell and Deuchar,[1] and Young and Griswold.[12] Hurwitt[7] reported four cases that were corrected by tying off the left superior vena cava.

CASE REPORT

The patient, an 18-year-old white male, was admitted in February, 1957, to the neurosurgical ward, General Hospital, Pretoria, as a case of head injury with left-sided hemiparesis. Consultation requested because of cyanosis led to his transference subsequently to the medical ward. The following history was obtained: His mother had had no severe illnesses during her pregnancy, labor was normal; persistent cyanosis had been observed at birth; during childhood he had become breathless during exertion more easily than the other children, who had also told him that he became blue.

According to his relatives his scholastic achievements had always been below average, with an I. Q. conforming to about 13 years of age. He had had a head injury a year previous to admission and was unconscious for 3 days. Three weeks previous to admission he became dizzy while doing fairly strenuous exercise and became very cyanotic. The house physician diagnosed a left-sided hemiparesis and referred him for further investigation.

Questioning in regard to the cardiovascular state revealed that the patient had fair exercise tolerance. He could easily trot for 100 yards. There was no history of congestive heart failure or nocturnal dyspnea, angina pectoris, or any retrosternal pain with or without exercise, but he became fatigued very easily.

The patient's family history showed that there were 2 sisters and 5 brothers, and that one brother, 8 years old, probably had a congenital heart lesion.

Physical examination revealed a well-developed male, with central cyanosis and definite clubbing of the fingers and toes. He had an exceptionally high palatal arch. The retinal veins were engorged.

TABLE I. MEASUREMENTS OBTAINED VIA LEFT CATHETER

CATHETER POSITION	BLOOD (VOLS. %)	OXYGEN (% SATURATION)	PRESSURE (MM.Hg)	MEAN PRESSURE (MM.Hg)
Aorta	12.1	90	87/55	65
Aorta (2)	12.1	90	80/57	65
Left ventricle (out)	12.2	90	80/10	45
Left ventricle (mid)	12.0	89	91/5	40
Left ventricle (in)	12.2	90	95.5/5	37.5
Left atrium (low)	11.6	87	—	7
Left atrium (mid)	12.8	93	—	8
Left atrium (high)	12.8	93	—	2
Persistent left superior vena cava	6.7	56	—	8
Femoral artery	12.3	91	77.5/57.5	65.5

TABLE II. MEASUREMENTS OBTAINED VIA RIGHT CATHETER

CATHETER POSITION	BLOOD (VOLS. %)	OXYGEN (% SATURATION)	PRESSURE (MM.Hg)	MEAN PRESSURE (MM.Hg)
Left pulmonary capillary	—	—	—	4
Left pulmonary artery	8.0	66	15/7	10
Main pulmonary artery	8.2	68	18/10	12
Right ventricle (out)	8.3	69	23/7	11
Right ventricle (mid)	8.6	71	23/7	11
Right ventricle (in)	8.3	69	24/6	11
Right atrium (low)	8.3	69	—	4.5
Right atrium (mid)	8.2	68	—	5.0
Right atrium (high)	8.0	66	—	7.5
Superior vena cava	8.6	71	—	5.0
Inferior vena cava	8.4	70	—	4.5

Cardiovascular System.—The pulse was 60 per minute. Blood pressure was 120/70 mm. Hg. There was no enlargement of the heart; the apex beat was of no definite type. There was a Grade 2 pansystolic murmur best audible at the apex. There was also an early soft blowing diastolic murmur at the apex. The second pulmonic sound was softer than the second aortic sound, and softer than one would have expected for his age. All the other sounds were normal.

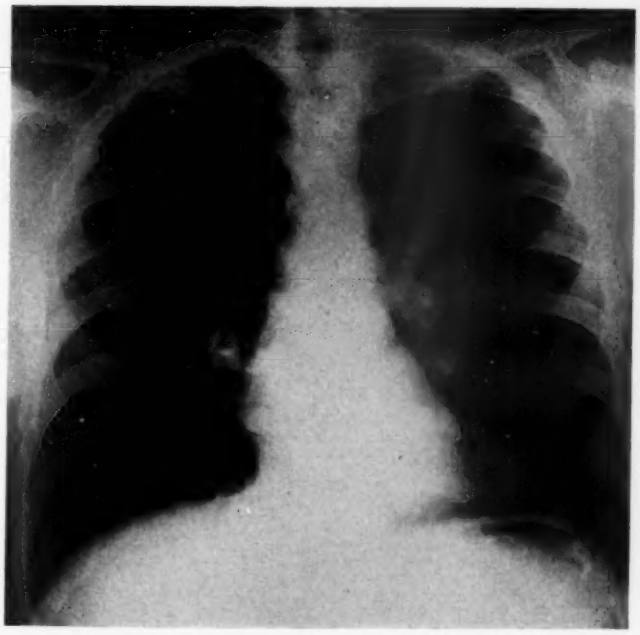

Fig. 1.—Normal size and shape of heart, and normal vascular markings.

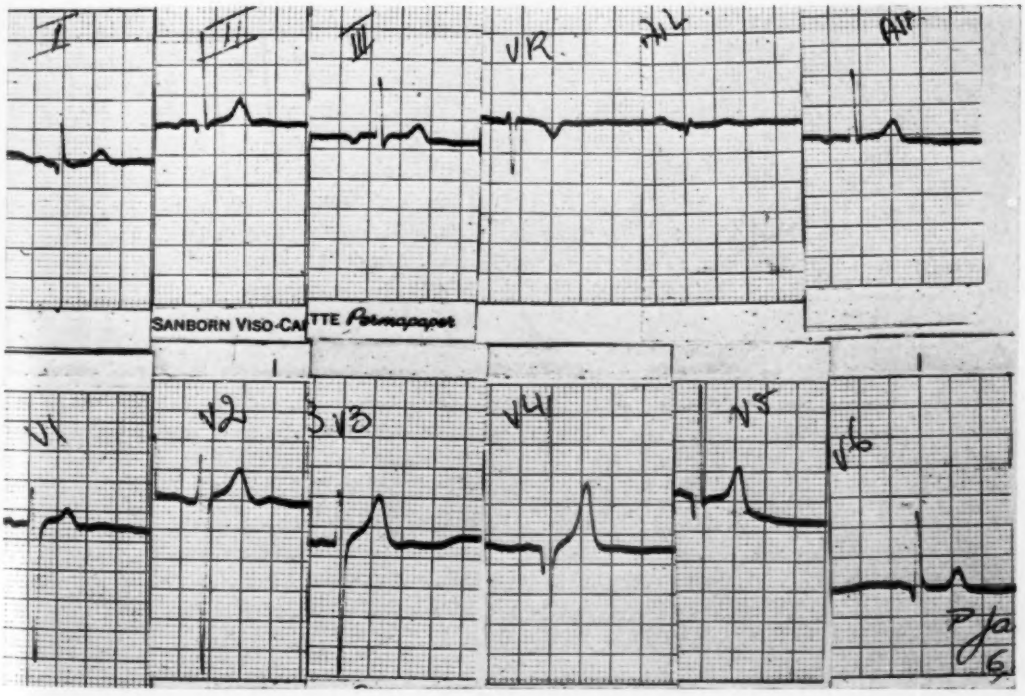

Fig. 2.—ECG. See text.

Laboratory examination revealed: hemoglobin of 18 Gm. (122 per cent), 6.5 million red cells, hematocrit of 55 per cent, 7,000 white cells with normal differential count. The roentgenfilm (Fig. 1) revealed normal size and shape of heart and normal vascular markings. The electrocardiogram (Fig. 2) showed inverted P waves in Leads III and aV_F and biphasic P waves in Leads II and aV_L; left ventricular hypertrophy Grade 1; concordant hypertrophy, delayed intrinsicoid deflection over the left precordial leads.

Fig. 3.—Catheter in left atrium and ventricle viewed from right side. The posteroanterior film was unfortunately not reproducible.

With these findings a diagnosis was made of left superior or inferior vena cava draining into the left atrium, on the basis of the central cyanosis with left ventricular hypertrophy, normal heart, and an exercise tolerance out of proportion with his cyanosis.

On Nov. 2, 1957, he was catheterized from the left arm, and as was expected, the catheter passed parasternally left into the left atrium, left ventricle, and aorta (Figs. 3 and 4; Table I). Three days later the catheter was passed from the right arm into the right atrium, right ventricle, pulmonary artery, and capillaries (Table II). It could not be shown that the left innominate vein was patent, but by passing the catheter down into the inferior vena cava from the right side, evidence was obtained that the inferior vena cava drained into the right atrium.

Surgical treatment was advised although we desired evidence of a patent left innominate vein of large size. The patient refused further hospital treatment at this stage.

On Aug. 5, 1958, he was readmitted to hospital for corrective surgery. Surgical exploration confirmed the persistent left superior vena cava draining into the left atrium. The left innominate vein was shown to be patent and a vessel of fair size; the right superior vena cava draining into the right atrium was present. The left superior vena cava was about one inch in diameter and drained into the left atrium just cranial to the left inferior and superior pulmonary veins. There was a very large hemiazygos vein present, about three-quarters inch in diameter. The cyanosis disappeared immediately after the anomalous vein was tied off. The patient at present (September, 1958) is in good condition.

COMMENTS

The basic hemodynamic disturbance following on this anatomic anomaly is increased blood flow through the left atrium and ventricle, decreased flow through the right-sided chambers, and partial bypass of the lungs. Clinical suspicion of the condition should be aroused in the presence of the following four features: (1) cyanosis out of proportion to the exercise tolerance, explained by the considerable bypass of unoxygenated blood; (2) increased flow through the mitral valve as indicated by the development of a diastolic murmur at the apex not explained by the signs of a mitral stenosis; (3) left ventricular hypertrophy established on physical examination or by electrocardiography, not explained on any other basis; (4) decreased flow through the pulmonary artery which may be revealed by an unexpectedly soft second pulmonic sound.

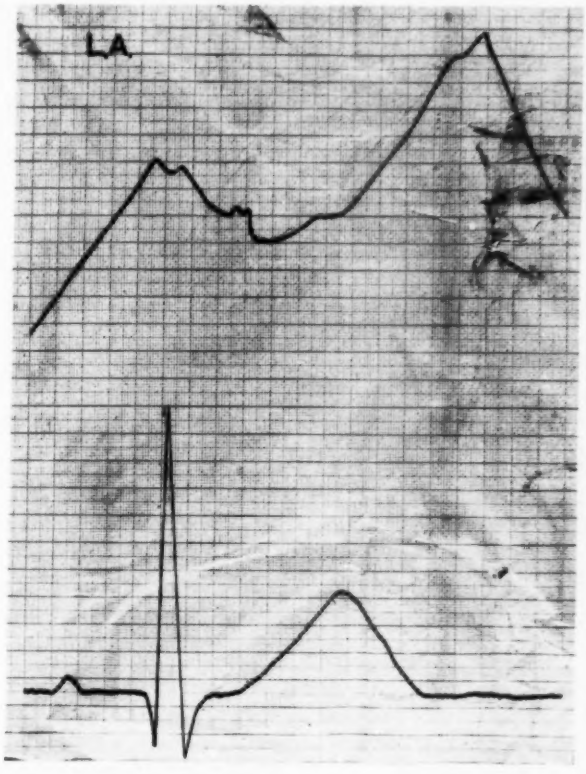

Fig. 4.—Pressure tracing of left atrium revealing prominent V wave.

The roentgenfilm is of assistance only in excluding other conditions; it does not contribute any positive feature. Confirmation is obtained by catheterization whereby direct entrance is gained to the left atrium and left ventricle when approached through the left arm veins, whereas the catheter shows normal sequence of right atrium and right ventricle when introduced from the right side. The pressure pattern provides further evidence in the prominent V wave on the graph obtained from the left atrium; this wave indicates an increased filling pressure, revealing the increased flow.

SUMMARY

A case of persistent left superior vena cava as an isolated anomaly was diagnosed clinically, confirmed on catheterization, and corrected surgically with excellent result. This is the second case, to our knowledge, to be reported.

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Antemortem Diagnosis of Metastatic Sarcoma to the Heart: A Case Report

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INTRODUCTION

Although Hurst[1] has reported a 20 per cent incidence of metastatic neoplasms to the heart, the clinical diagnosis of such metastases is a rarity. In his review of tumors of the heart, in 1951, Prichard[2] listed only 20 cases in which the antemortem diagnosis of metastatic carcinoma to the heart was made. There were, however, only 5 instances of the antemortem diagnosis of sarcoma involving the heart.

The incidence of cardiac metastasis has increased in recent years from the 2 to 10 per cent reported in the earlier literature[3,4] to 20 per cent in the more recent series.[1,5-7]

Metastatic involvement of the heart can be diagnosed only if the possibility is kept in mind. It should always be considered in patients with known malignancy when the following clinical manifestations develop: (1) progressive congestive heart failure; (2) evidence of persistent pericarditis for many weeks as evidenced by a persistent friction rub, and/or pericardial effusion; (3) signs of constrictive pericarditis; (4) cardiac arrhythmias; and (5) sudden death.

CASE REPORT

F. F., a 57-year-old Negro woman, was first admitted to the District of Columbia General Hospital in August, 1957, with a one month's history of left hip pain radiating down the posterior thigh to the heel and great toe, with associated swelling of the left leg. There was evidence of deep vein thrombophlebitis, and treatment consisted of anticoagulants, bed rest, and elevation. An extensive medical work-up including x-ray studies (intravenous pyelography, gastrointestinal series, and barium enemas), lumbar puncture, and blood chemistries were completely unrevealing. During the course of her hospitalization she developed upper gastrointestinal bleeding, and anticoagulants were discontinued. The patient left the hospital against medical advice after approximately two weeks.

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Four months later she was readmitted to the orthopedic service because of severe hip pain. A repeat lumbar puncture was normal. Intravenous pyelograms, gastrointestinal series, and barium enema were reported as normal, and bone survey was reported as showing no abnormalities. Hematology consultation was obtained and examination of the bone marrow aspirate was compatible with a chronic inflammatory reaction with a marked decrease in bone marrow iron.

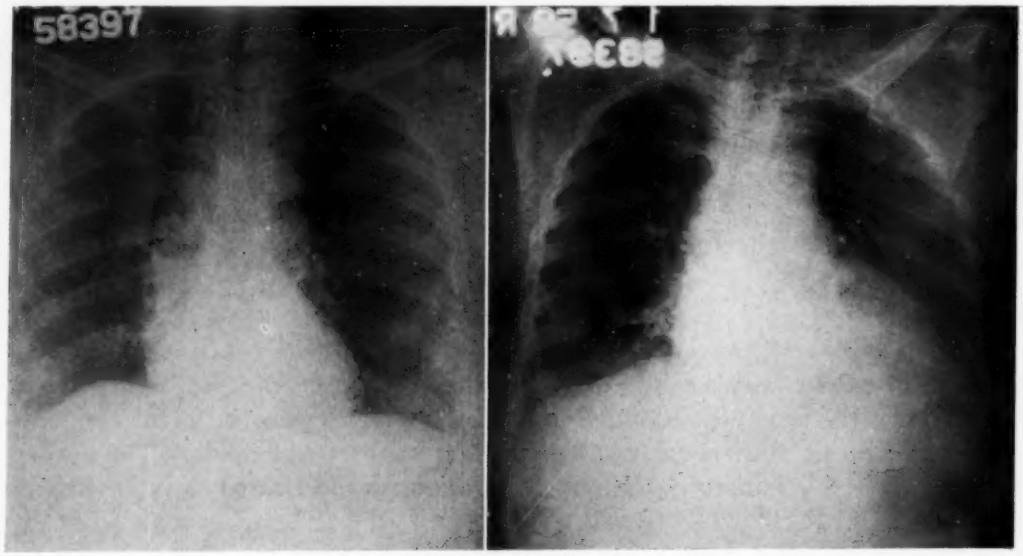

Fig. 1.—X-rays of the chest showing the change in cardiac size and contour between initial and final admissions.

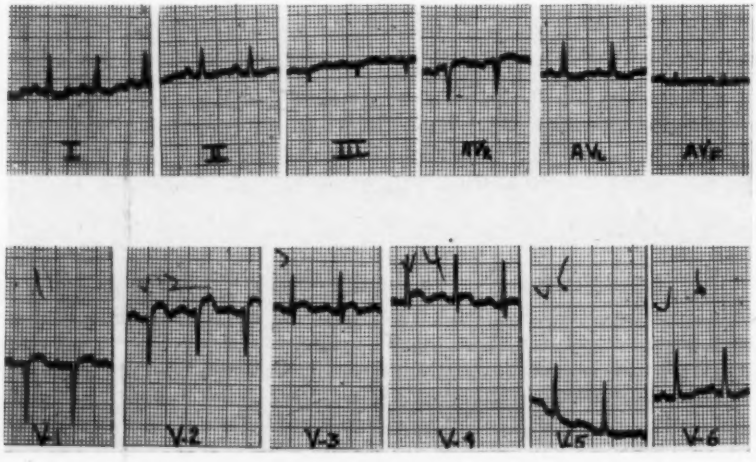

Fig. 2.—Electrocardiogram showing elevated S-T segments from Lead V_1 through V_4, with inversion of the T waves following the elevated S-T segments.

Electromyography revealed a "complete nerve lesion" of the left quadriceps and the anterior tibial muscles. Hematocrits were consistently 33-34 mm. (Wintrobe). Repeat blood chemistries, including total protein, albumin and globulin ratio, alkaline phosphatase, and uric acid, were all within normal limits. Multiple urinalyses showed persistent one-plus albuminuria, and repeated Bence-Jones determinations of protein were negative.

Her left hip pain suddenly became more severe and was associated with a dull, nonradiating left anterior chest pain. The chest pain subsided spontaneously but the hip pain persisted. Her blood pressure, which was usually 170/80 mm. Hg, was now recorded as 120/80 mm. Hg. On the following day an electrocardiogram was taken and revealed an irregular rhythm with a heart rate of 170 beats per minute and inversion of the T waves across the precordium. A repeat electrocardiogram later that day revealed a Q wave in Lead V_1 with elevation of the S-T segment in Leads V_1 through V_3. She was seen by the medical consultant and transferred to the medical ward.

Physical examination at this time revealed a well-developed, well-nourished, 57-year-old Negro woman appearing chronically ill, lying on her right side and complaining of pain in her left hip. Her temperature was 99° F., pulse 120 (and regular), respirations 24, and blood pressure 130/98 mm. Hg. The positive physical findings were limited to the heart and extremities. The heart was enlarged to percussion. There was a sinus tachycardia. The second aortic sound was louder than the second sound in the pulmonic area; the first mitral sound was louder than the second. There was a "scratchy," Grade 2 aortic systolic murmur radiating to the neck. There were flexure contractures of the hips bilaterally; there was tenderness of the calf on the left with a positive Homan's sign. The Lowenberg test was positive; the left leg was measurably larger than the right in circumference. There was pain in the left hip, with point tenderness over the greater sciatic notch.

A portable chest film revealed clear lung fields, and the costophrenic angles showed no roentgenographic evidence of pulmonary infarction or pleural effusion (Fig. 1).

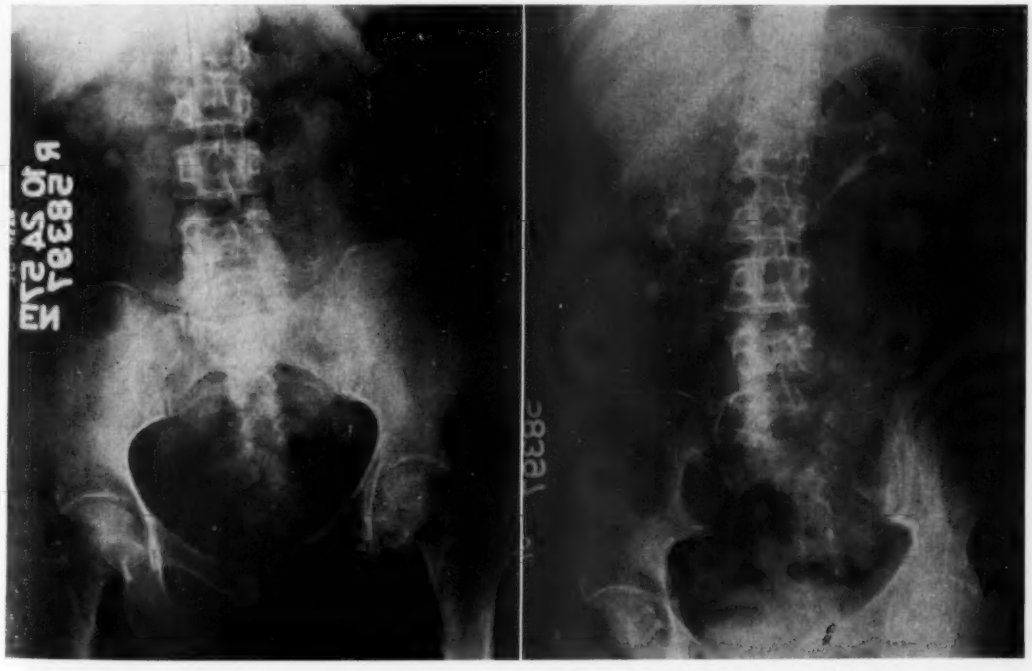

Fig. 3.—X-rays of the pelvis showing mass in the area of the fifth lumbar vertebra, with lysis of this vertebra and its transverse process and a displacement of the left ureter by the pelvic mass.

A repeat electrocardiogram revealed a heart rate of 132; the P-R interval was 0.16 second; the QRS complex was 0.06 second in duration. There were elevated S-T segments from Lead V_1 through V_4, with inversion of the T waves following elevated S-T segments (Fig. 2). The impression at that time was that the patient had chronic deep venous disease with possible pulmonary embolism and/or myocardial infarction and peripheral neuropathy, etiology undetermined.

Review of the x-ray studies revealed a pelvic mass in the area of the fifth lumbar vertebra, with lysis of this vertebra and its transverse process and a displacement of the left ureter by a pelvic mass (Fig. 3).

On the following day a pericardial friction rub developed and the electrocardiogram revealed a rapid auricular fibrillation with a ventricular rate of 210 beats per minute. Her skin was cold

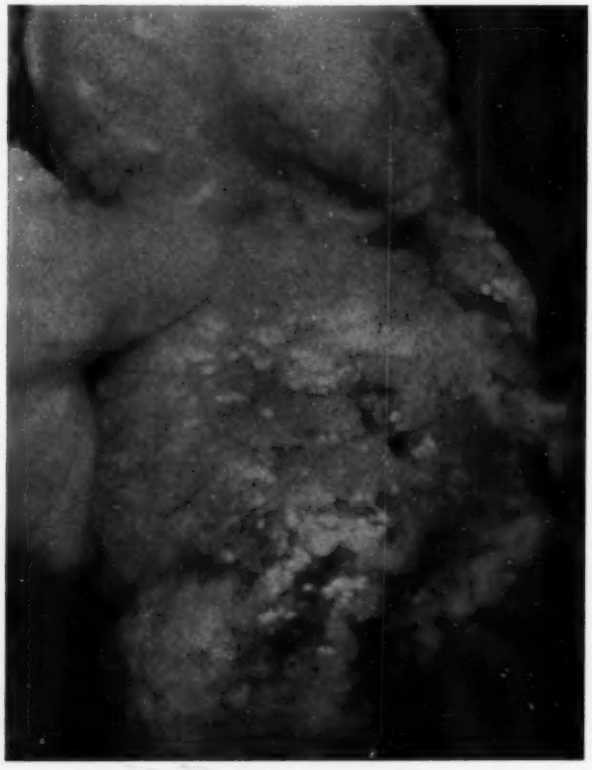

Fig. 4.—Large mass of tumor excised from pelvis at time of postmortem examination.

and was diaphoretic; she was moderately dyspneic and complained of chest pain which was relieved by holding her breath. Carotid sinus stimulation slowed the heart rate to approximately 96 beats per minute. She was given intravenous Cedilanid. Anticoagulant therapy for the deep venous disease was discontinued, and protamine-sulfate was given intravenously because of the possibility of a hemorrhagic pericarditis. Later that evening a repeat electrocardiogram revealed a flutter-fibrillation, but by the next morning, following intramuscular digoxin therapy, she had reverted to a normal sinus rhythm. At this time the diagnosis of cardiac metastasis secondary to a sarcoma in the pelvis was strongly considered because of persistent left ventricular failure, persistent arrhythmias on therapy with digitalis, pericarditis, and the lytic lesion in the pelvis. She had a rapid downhill course and expired.

Postmortem Examination.—Autopsy revealed a retroperitoneal fibrosarcoma originating in the soft tissues of the left lumbar paravertebral region and infiltrating the left half of the fifth lumbar vertebra (Fig. 4). In addition, there was involvement of the upper sacrum on the left, the anterior ligament of the spinal canal, the left paravertebral and psoas muscles, the regional lymph nodes, the left iliac vein, the femoral nerve roots arising from the lumbar to the first sacral segment, the left iliac artery and the left hypogastric artery, and the adventitial layer of the left ureter. There were metastases to the lungs, kidney, and heart. The pericardium and epicardium were fibrosed, and there was 50 c.c. of bloody pericardial fluid with a fibrinous pericarditis. The

sarcoma had encroached upon and infiltrated the coronary arteries, with resultant narrowing of their lumina. The origin of the branch to the right posterior wall and left anterior wall was completely occluded by a 3 by 3 cm. nodular metastasis (Fig. 5). Metastases were also seen throughout the myocardium and all aspects of the ventricles, including the upper portion of the septum. There was a 5 by 4 cm. nodular metastasis in the right ventricular endocardium.

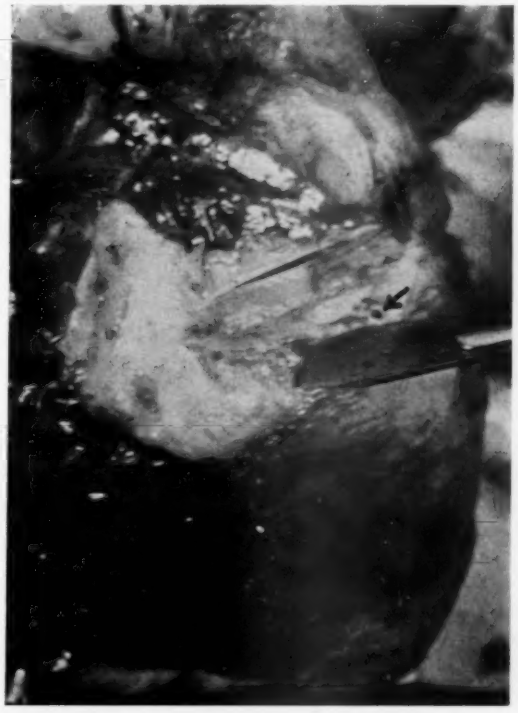

Fig. 5.—Posterior wall of the heart demonstrating the large nodular metastasis and the occlusion of the coronary artery.

DISCUSSION

Neoplasms of the heart may be divided into two categories, primary and secondary. Primary tumors of the heart are 20 to 40 times less frequent than the secondary or metastatic variety. We are concerned primarily with the secondary or metastatic neoplasm.

In Prichard's recent report[2] the antemortem diagnosis of cardiac metastases was made in 20 patients. There is evidence, however, that the frequency of proved metastasis to the heart has increased in recent years (Table I). In the series reported by Scott and Garvin,[4] in 1939, there were 1,082 patients with proved malignancies. Out of this group, 118 had metastases to the heart and/or parietal pericardium, giving an incidence of 10.9 per cent. Thirty-seven of these were sarcomas (including reticulum cell and lymphosarcoma). In Burnett's series[8] there were 14 cases of sarcoma and only one patient had cardiac metastasis (Table II).

This gradually increasing frequency of proved cardiac metastasis may be attributed to an increased interest and to a closer search at autopsy for metastatic lesions. In addition, with better supportive care, patients are living longer and have more opportunity to develop cardiac metastases.

TABLE I. INCIDENCE OF CARDIAC METASTASIS

AUTHOR	DATE	MALIGNANCY (NUMBER OF CASES)	NUMBER OF CASES SHOWING CARDIAC METASTASES	PERCENTAGE
Bryant[2]	1902	2,492*	9	0.4
Symmers[2]	1917	298	5	1.6
Bardenheuer[2]	1924	1,275*	30	2.3
Burke[2]	1934	327	14	4.3
Benjamin[2]	1939	40,000*	—	0.5
Scott and Garvin[4]	1939	1,082	118	10.9
Dimette[2]	1950	455	38	8.3
Prichard[2]	1951	4,375	146	3.4
Burnett[3]	1953	288	52	18.0
DeLoach[5]	1953	980	136	13.9
Cohen[6]	1955	315	65	20.6

*Represents total number of autopsies rather than number of malignancies.

TABLE II. COMPARISON OF CARDIAC METASTASES BETWEEN CARCINOMA AND SARCOMA

AUTHOR	CARCINOMA		SARCOMA	
	NUMBER	PERCENTAGE	NUMBER	PERCENTAGE
Scott and Garvin[4]	985	9.0	37	37.8
Prichard[2]	102	2.3	26	0.6
Burnett[3]	116	15.0	14	7.0
Cohen[6]	65	20.6	—	—

In spite of the more frequent diagnosis of metastatic disease to the heart, there appears to be several factors which keep the frequency of metastases to the heart lower than in other organs. Prichard speculates that one of these may be the strong kneading action of the heart. He also mentions the metabolic peculiarities of striated muscle, the rapid blood flow, and the restricted lymphatic connections of the heart as mechanisms which might prevent more frequent cardiac involvement.

Metastasis to the heart occurs via three routes: by the blood stream as embolic phenomenon, by the lymphatics, or by direct extension. The right side of the heart appears to be involved more frequently regardless of the number of lesions or the histologic type. The lesion usually appears as a discrete nodule which is similar to metastatic lesions elsewhere in the body. By gross examination the primary site usually cannot be determined. It may enlarge sufficiently to encroach upon the ventricular chambers and produce congestive heart failure on

that basis. A nodular lesion may constrict a vessel by its location and growth, and may produce signs, symptoms, and electrocardiographic evidence of myocardial infarction.

Although metastases to the heart are usually silent, the metastatic nodule may be anatomically located so that it interferes with the conducting system of the heart. When this occurs any of the cardiac arrhythmias may occur. The most common are auricular fibrillation and auricular flutter, which may appear as transient paroxysms and which will later persist. Atrioventricular block of all degrees may develop. The patient may die a sudden death. The metastases may produce a picture of progressive congestive heart failure manifested by a ventricular gallop and the findings of left and right heart failure. The electrocardiogram may show only nonspecific T-wave abnormalities, or may show evidence of pericarditis, low voltage, or the various arrhythmias already mentioned.

Pericardial lesions may produce a pericarditis with a bloody pericardial effusion large enough to cause cardiac tamponade. When deep venous disease develops as a complication in a patient with a malignancy, the use of anticoagulants in the presence of a friction rub and evidence of pericardial effusion is strongly contraindicated. This is one instance in which the correct diagnosis of metastasis to the heart is important. The endocardium is rarely involved and it is extremely rare to find metastatic endocarditis.

Finally, it is important to keep in mind the possibility of metastatic heart disease when a patient with a known malignancy has persistent refractory congestive heart failure, arrhythmias, or pericarditis which is not readily explained.

SUMMARY

The case of a 57-year-old patient with suspected primary sarcoma of the pelvis and antemortem diagnosis of cardiac metastasis is presented. Postmortem examination revealed a fibrosarcoma of the pelvis with cardiac involvement. One of the metastatic nodules was found encompassing and constricting the descending branch of the left coronary artery, producing electrocardiographic evidence of myocardial infarction. A review of the clinical manifestations and pathology of metastases to the heart is also presented.

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Dissecting Aneurysm of Coronary Artery Producing Myomalacia and Death

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Arteriosclerosis is by far the most common underlying cause of thrombosis and obstruction of the coronary arteries, sometimes in connection with hemorrhage into an atheromatous plaque.[1,9,11] Other less common causes of occlusion are embolism, inflammation including syphilis and rheumatic fever, thromboangiitis obliterans, polyarteritis nodosa, etc.[7] However, aneurysms[8,10,13,14] and, specifically, isolated dissecting aneurysms causing occlusion of the coronary arteries are extraordinarily rare; only two of the latter variety have been mentioned briefly in the American literature[4,21,22] and only three cases are published elsewhere.[12,17]

CASE REPORT

The case to be discussed is that of a 38-year-old housewife who had the classic clinical picture of acute myocardial infarct with fatal outcome secondary to dissection of blood between the external layers of the right coronary artery in an arterial system which showed no signs of arteriosclerosis.

The patient was admitted to the Jewish Hospital on March 23, 1958, because of severe substernal pain with radiation to the back, associated with numbness of both arms. The chest pain had been preceded by several hours of nausea and vomiting. She had been seen by her family physician at home shortly after the onset of pain. He found that she was pale, sweating, and complaining of severe pain, requiring morphine sulphate, grains 3/8, hypodermically for relief. Pulse was 100 and regular; blood pressure was 80 mm. Hg systolic, the diastolic being unobtainable. At the time of admission to the hospital one hour later she was comfortable and her color was good. Blood pressure was 110/80 mm. Hg; pulse was 150 with an irregular irregularity. Heart sounds were of good quality, and the chest was clear. Peripheral pulsations were normal throughout.

The admission electrocardiogram (Fig. 1) showed atrial fibrillation with very marked elevation of the S-T junction in precordial leads. An electrocardiogram taken one-half hour later (Fig. 2) showed sinus rhythm with elevation of the S-T junction in Leads I and V_L. In the precordial leads, the R wave had disappeared in V_2, V_3, V_4, and V_5, with marked elevation of the S-T junction in these leads. Admission urinalysis showed a specific gravity of 1.020, protein 10 mg./100 ml., occasional white blood cells, and several finely granular casts. Red blood count on admission was 4.7 million, and white blood count was 16,100, with 77 per cent neutrophils,

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10 per cent lymphocytes, 11 per cent myelocytes, and 2 per cent eosinophils. Serum glutamicoxalacetic transaminase was 192 units on the day of admission, 368 units on the next day, 137 units on the second hospital day, and 33 units on the eighth hospital day. Blood urea nitrogen was 17 mg./100 ml. Serologic test for syphilis was negative.

On admission to hospital the patient was placed in an oxygen tent. Anticoagulant therapy was initiated with intermittent intravenous injection of heparin and maintained with Tromexan and Dicumarol. By March 26, prothrombin had fallen to 25 per cent of normal and was maintained between 20 and 30 per cent of normal. Heparin therapy was discontinued on March 26. On March 25, the patient experienced onset of normal menstruation, perhaps with slightly more bleeding than usual. She was comfortable and free of pain until March 30, when she again complained of severe retrosternal pain radiating through to the back. At this time she was found to have tachycardia, with a blood pressure of 127/110 mm. Hg. Narcotics were required for relief. An electrocardiogram showed no evidence of extension of the infarction. During the next two days she continued to complain of pain.

On the evening of April 1, she was found to be anxious and dyspneic. Blood pressure was 70 mm. Hg by palpation. There was no evidence of pericardial effusion or of congestive heart failure. Despite rapid digitalization with lanatoside, intramuscular administration of prednisolone, and intravenous administration of levarterenol bitartrate, her course continued downhill, with increasing shock and signs of congestive failure. She died at 2.30 A.M. on April 2, 1958.

Past medical history disclosed that she had been treated for mild hypertension and recurrent headaches prior to her first admission to Jewish Hospital on March 13, 1952, for sudden loss of consciousness which had occurred ten days following the delivery of a child. Signs of meningeal irritation were found at this time, and lumbar puncture revealed grossly bloody cerebrospinal fluid. On March 20, 1952, a right carotid angiogram revealed a small saccular aneurysm of the internal carotid artery, approximately 1 cm. below the bifurcation into the middle and anterior cerebral arteries; it was ligated in a two-stage procedure on March 20 and 21, 1952. Following convalescence, she felt well. At occasional visits to her physician, her blood pressure was found to be approximately 150/90 mm. Hg. On Oct. 17, 1955, she was admitted again to Jewish Hospital for therapeutic interruption of a 3-month pregnancy. Blood pressure at this time was 150/95 mm. Hg. Urinalysis showed a specific gravity of 1.029 and no abnormal findings. The blood count was normal except for slight anemia. Hysterotomy and ligation of Fallopian tubes was carried out on Oct. 20, 1955.

Autopsy Findings.—On external inspection there was no edema of the lower extremities noted. On opening the abdomen, 20 c.c. of clear fluid was found. In the left hemithorax there was 1,200 c.c. of bloody fluid, and in the right side, 800 c.c. of similar fluid. The pericardial cavity contained 20 c.c. of clear straw-colored fluid. The heart weighed 400 grams, and the thickness of the left ventricular wall was 10 to 20 mm., while that of the right side was 5 to 8 mm. In the epicardium an ecchymotic area of 3 by 2 cm. was found covering the posterior wall of the left ventricle. On opening the heart, hypertrophy of the left and right ventricles was found; it was especially massive on the left side. Extensive areas of infarction were found in the interventricular septum and in the lateral and posterior walls of the left ventricle. The aorta in its entire course was smooth and apparently of normal elasticity. There was no evidence of atheromatous formation or calcification in any part of this vessel. Complete occlusion of the right coronary artery was found near the ostium. The two major branches of the left coronary artery were free of pathology. The kidneys together weighed 300 grams and had a smooth surface, without any additional abnormalities being described. On the internal carotid artery, on the base of the brain on the right side, two silver clips were found which obviously represented residuals of the surgical procedure which had been carried out 6 years earlier for aneurysm at this location. Noticeable was a fibrous segment of the artery which represented organization of this thrombosed aneurysm. The microscopic inspection of the right coronary artery showed between the media and adventitia a recent hematoma of considerable extent which had produced an almost complete compression of the lumen of the artery, decreasing it to a slit-like opening (Fig. 3). At the same time there was obvious organization going on in the space between the adventitia and media, indicating that the hemorrhagic process was recurrent in nature, and that the initial dissection must have occurred several weeks previously. The dissection in some places had also entered between the layers of the

adventitia itself, and certain cross sections showed that the dissection almost completely encircled the lumen. In the periadventitial tissue was a cellular infiltrate which consisted mostly of round cells, the overwhelming majority of which were lymphocytes. There was, however, an admixture of eosinophilic leukocytes, which, in certain areas, may have represented as much as 40 per cent of the total cell infiltrate. In general, the infiltrate was not very heavy but it was found in all parts of the periadventitial tissue. This periadventitial tissue showed, also, very numerous vascular channels far in excess of the number of vessels seen normally surrounding the coronary arteries. Definitive defects were found in the elastic tissue of the artery (Fig. 4).

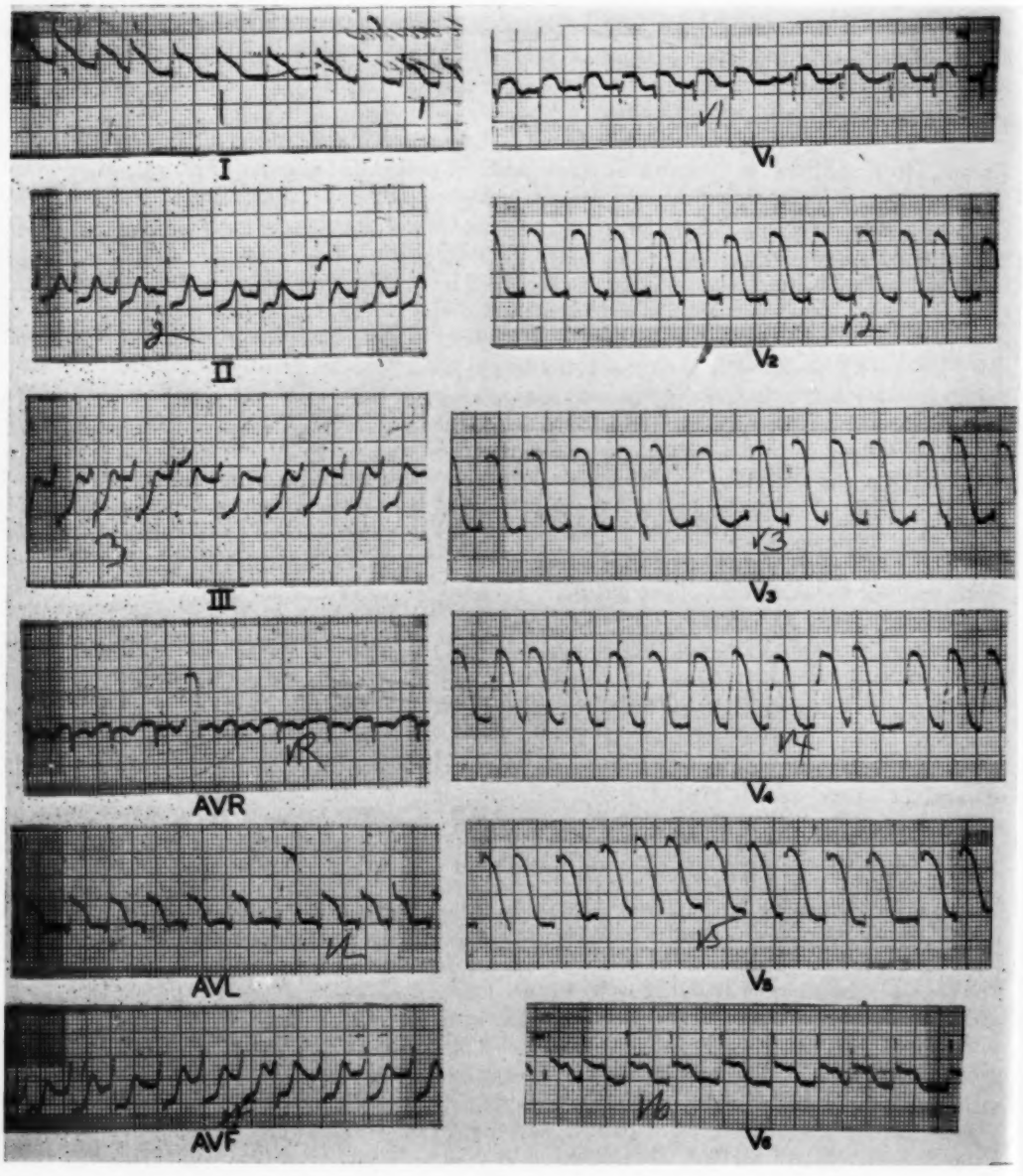

Fig. 1.—Admission electrocardiogram recorded at 2:00 P.M., March 23, 1958, showing atrial fibrillation and marked elevation of the S-T junction in precordial leads.

The microscopic examination of the myocardium showed myomalacia in three different stages of development. There was a rather recent area, immediately under the endocardium, which showed eosinophilic discoloration of fibers, with partial loss of striation and nuclear staining. This was obviously an infarct of only a few hours' duration. There were also areas of recent infarction of several days' duration, with outpouring of leukocytes in the zone of demarcation. Finally, there were extensive areas of subacute organizing infarct formation, estimated to be of at least three weeks' duration in view of the partial organization of the necrotic tissue and the presence of numerous capillaries and proliferating fibroblasts. Careful examination of the aorta and other large and small vessels failed to reveal any appreciable degree of arteriosclerosis.

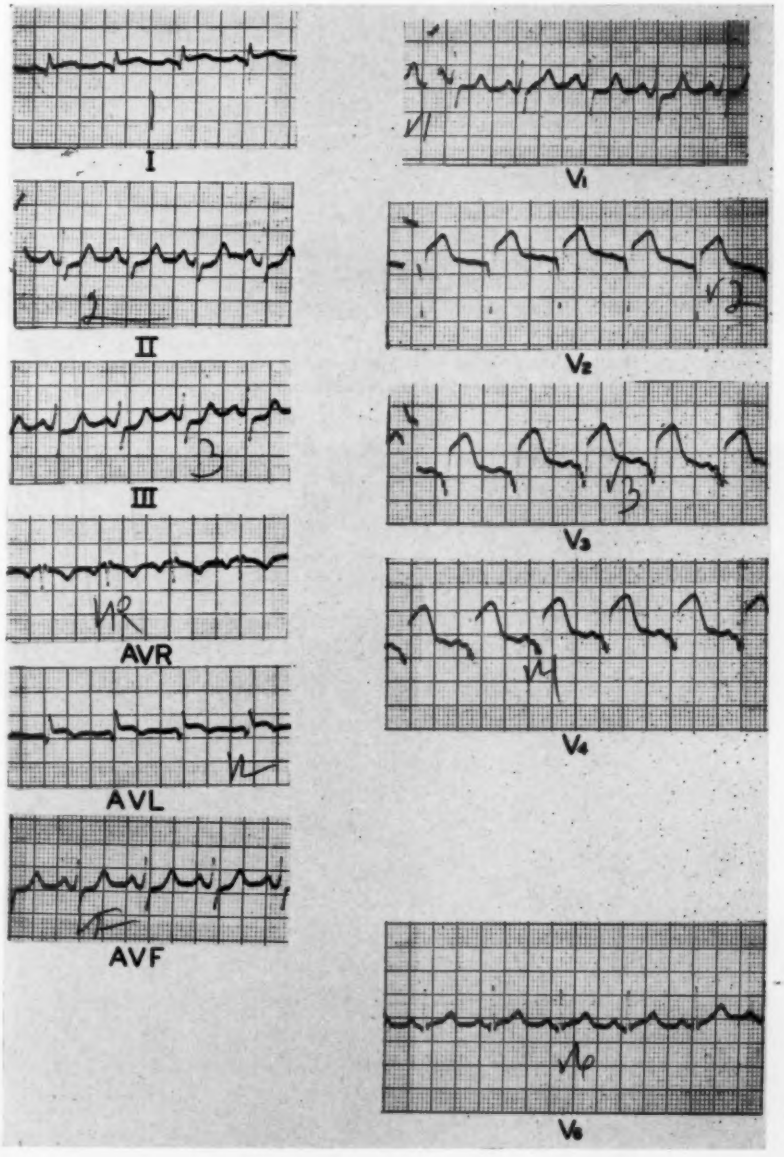

Fig. 2.—Electrocardiogram recorded at 2:35 P.M., March 23, 1958, one-half hour after the admission electrocardiogram shown in Fig. 1.

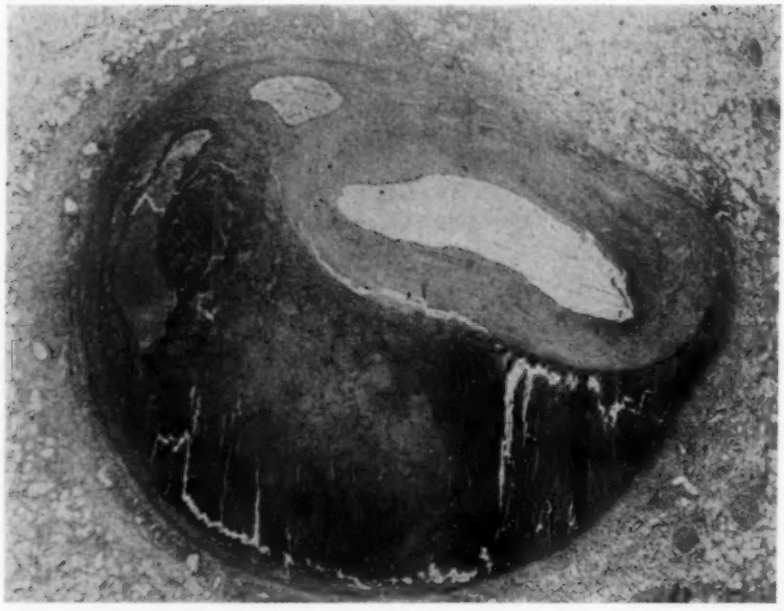

Fig. 3.—Massive dissection between the external layers of right coronary artery. (Hematoxylin-eosin stain.)

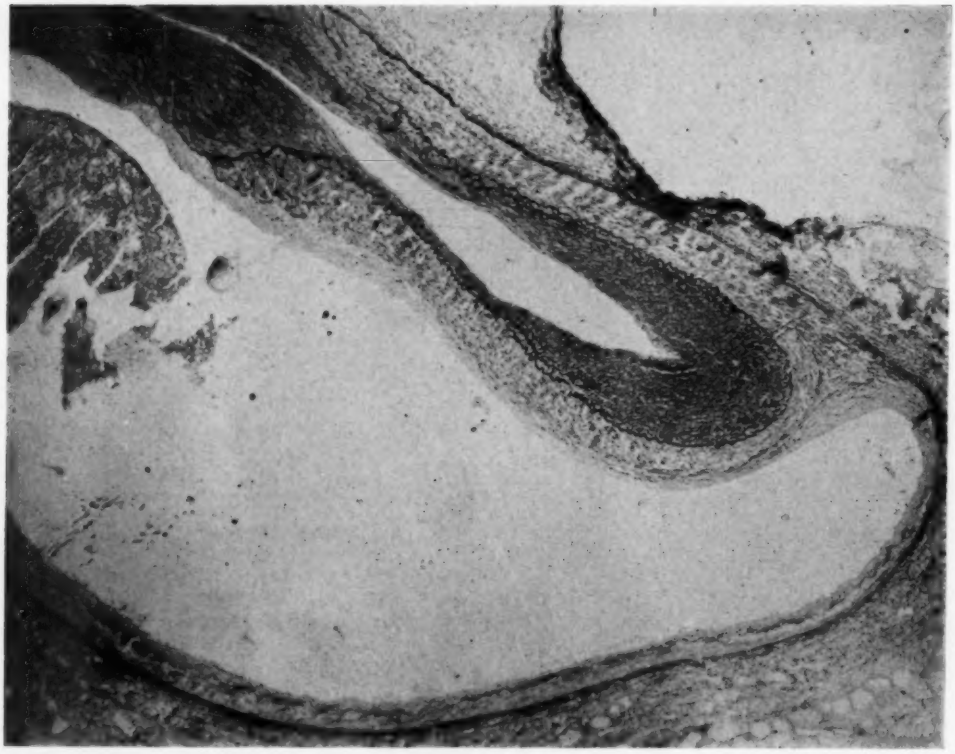

Fig. 4.—Defects in the elastic fibers are obvious in the media of the vessel. (Gridley stain.)

DISCUSSION

Uehlinger[17] described two fatal instances of isolated dissecting aneurysm of coronary arteries in healthy men in their forties, subsequent to considerable exertion in the Swiss mountains. His second case has many features which are similar to the ones seen in the case reported by us. White,[22] in discussion in a clinicopathologic conference, mentioned dissecting aneurysms of coronary arteries, but further details are not available.[23] Glendy, Castleman and White,[4] in reviewing cases of dissecting aneurysm at the Massachusetts General Hospital, found one instance from 1902 of a "small slit" in the left anterior descending coronary artery in the absence of aortic dissection. Microscopic examination was not reported. Pretty,[12] in 1931, reported a dissecting aneurysm of a coronary artery in a 42-year-old woman which he thought "sufficiently rare . . . to merit publication." No anatomic details were given. Other authors have reported dissection in walls of atheromatous coronary arteries,[1,9,11,20] and extension of aortic dissecting aneurysm into coronary arteries.[5,15,18] Isolated dissecting aneurysms in other systemic arteries and in the pulmonary arteries have been described occasionally.[5,6]

Thus, in the world literature there are only five previously described cases of true isolated coronary dissection in the absence of arteriosclerosis; microscopic control was done in only two of these.[17] One has to ask why the phenomenon should be so extraordinarily rare.

In the first place, dissection is a phenomenon apparently intimately related to arteriosclerosis. Whereas, Shennan,[15] Hirst,[5] and others[16] have shown that the perforation of the intima generally does not occur through an atheromatous plaque, it is equally true that occurrence of dissection is much more common in older people, in whom the media has suffered from the wear and tear of life as compared with intact aortas of younger persons. Secondly, the mechanism is apparently the following: small tears in the intima occur, from which deeper layers become involved, and the tunnel is formed by the systolic blood pressure within the layers of the media or between media and adventitia. Whether certain embryologic and anatomic differences in the structure of the coronary arteries are contributory to the resistance of these arteries to the formation of aneurysms in general and to dissecting aneurysms can be only surmised. The defect seems to be located generally in the media and not in the intima.

Therefore, it becomes likely that in the case under discussion a congenital abnormality existed in the wall of at least two vessels. Other congenital defects have been reported in association with intracranial aneurysms.[2,3,19] Evidence exists of the presence of the cerebral aneurysm which was ligated six years prior to the occurrence of the dissecting aneurysm. The absence of previous symptoms which could be related to the coronary arteries, and the absence of any arteriosclerotic changes strongly suggest that, possibly, a weakened media gave way to some sudden minor increase of blood pressure.

Uehlinger[17] is rather dogmatic about the role of exertion in the two cases which he describes, but this certainly is not a universally accepted mechanism for the development of dissecting aneurysms, although stressed by Shennan.[15]

Dissecting aneurysms are notoriously frequent in the aorta, and from the aorta they may extend into the major branches—specifically, into the internal carotid arteries or any of the major branches of the abdominal aorta. Extension from dissecting aortic aneurysms into the coronaries is not a common occurrence, for the very simple reason that the tear in the aorta customarily occurs above the coronary ostia.[5,15]

The absence of atherosclerosis in our patient deserves comment. Hemorrhage into an atherosclerotic coronary artery plaque is well recognized and not infrequent.[11] Authors have commented on obstruction of the lumen produced by intimal hemorrhages of this type, even in the absence of intravascular thrombosis.[20] In the present case, hemorrhage was not into the intima but definitely into the media of the vessel. The classic clinical picture of acute myocardial infarction was produced because the hemorrhage was extensive enough to occlude the vessel completely. Shennan[15] stresses the possible role of stress in precipitating intramural bleeding in dissecting aneurysms. Possibly, the vomiting in our patient prior to the onset of symptoms furnished this stress. It is known that during straining marked changes in blood pressure and blood flow occur. An alternate interpretation is, of course, that the vomiting was part of the clinical syndrome of myocardial infarction.

In our patient the initial dissection must have occurred several weeks prior to death, even though the clinical history appears to be shorter. The status of the organization in the vessel and the organization of the myomalacia clearly indicated that at least two to three weeks had passed between the initial onset and the final outcome. We visualize the penetration of the blood between media and adventitia close to the ostium of the vessel, which either may have compressed the artery to a degree sufficient to produce myomalacia or may have separated branches of the main stem from the former, producing anoxia and necrosis of the muscle tissue. The process must have progressed distally and terminated when the internal layers of the artery were almost completely surrounded by blood which then produced an obstacle to the circulation which was not further compatible with life. Whether the clinically marked episodes are related to steps in this development in the sense that the involvement of major branches produced a new catastrophe is hard to say, but from the appearance of the myocardial necrosis it can be clearly stated that at least three major and independent attacks of necrosis occurred, one approximately two to three weeks prior to death, one several days up to one week prior to death, and the last one several hours to one or two days prior to death. The mechanism of necrosis is clearly obstruction of the blood flow.

SUMMARY

A case of one dissecting aneurysm restricted to the right coronary artery in a 38-year-old woman is reported. The arterial system showed no arteriosclerosis. Several years prior to death the patient had an aneurysm of the middle cerebral artery ligated, indicating the possibility of a congenital vascular abnormality in at least two vessels. Dissecting aneurysm of the coronary artery is an exceptional cause of myocardial infarct.

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Announcement

THE AMERICAN COLLEGE OF CARDIOLOGY will hold its EIGHTH ANNUAL CONVENTION at the Benjamin Franklin Hotel, Philadelphia, Pa., May 25-29, 1959, according to an announcement by Gabriel F. Greco, M.D., Ozone Park, N. Y., member of the Publication Committee.

The program covers recent trends in medical and surgical progress in cardiology. John S. LaDue, M.D., New York, is National Chairman, Program Committee. Robert Glover, M.D., Philadelphia, is Advisory Chairman to the local committee in charge of convention arrangements. Seymour Fiske, M.D., New York, is National Chairman. Claude S. Beck, M.D., Ohio, is moderator of a scientific session on surgical problems in coronary and valvular heart disease, featuring, among many aspects, new techniques, use and abuse of pump oxygenators, pacemakers, and the evaluation of postoperative syndromes. Ashton Graybiel, M.D., Florida, has arranged a special session on the newer challenges in aviation medicine and the newer aspects of space cardiology. There will be scientific sessions devoted to phonocardiography, ballistocardiography, metabolism, and therapy. Fireside conferences will allow audience participation in the solution of clinical and research problems.

Further information may be obtained from the Secretary, Dr. P. Reichert, American College of Cardiology, Empire State Bldg., New York 1, N. Y.